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DRINKING WATER CRITERIA DOCUMENT FOR POLYCHLORINATED BIPHENYLS (PCBS)

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DISCLAIMER

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LIST OF ABBREVIATIONS

AAH	Aryl hydrocarbon hydroxylase
BCF	Bioconcentration factor
BHC	Benzene hexachloride
BOD	Biologic oxygen demand
bw	Body weight
CAS	Chemical Abstracts Service
CB	Chlorinated biphenyl
d	Deuterium
DCB	Dichlorinated biphenyl
DEN	Diethylnitrosamine
DMBA	Dimethylbenzanthracene
DMN	Dimethylnitrosamine
DNA	Deoxyribonucleic acid
DP	Diphenyl
DWEL	Drinking water equivalent level
EROD	Ethoxyresorufin o-deethylase
eV	Electron volts
EXAMS	Exposure Assessment Modeling System
2-FAA	N-2-fluoroenylacetamide
GC	Gas chromatography
GI	Gastrointestinal
gmw	Gram molecular weight
H	Proton
HA	Health Advisory
HCB	Hexachlorinated biphenyl
HPLC	High performance liquid chromatography
I.D.	Internal diameter
i.p.	Intraperitoneal
K_{ow}	Octanol water coefficient
KC	Kanechlor
LD_{50}	Lethal dose for 50% of recipients
LOAEL	Lowest-observed-adverse-effect level

DEFINITIONS

Isomers	PCBs having the same molecular weight and chlorine number but with the chlorines substituted differently
Congeners	PCBs having different numbers of chlorines

TABLE II-1

Numbering of PCB Isomers*

No.*	Structure	CAS No.
Monochlorobiphenyls		
1	2	2051-60-7
2	3	2051-61-8
3	4	2051-62-9
Dichlorobiphenyls		
4	2,2'	13029-08-8
5	2,3	16605-91-7
6	2,3'	25569-80-6
7	2,4	33284-50-3
8	2,4'	34883-43-7
9	2,5	34882-39-1
10	2,6	33146-45-1
11	3,3'	2050-67-1
12	3,4	2974-92-7
13	3,4'	2974-90-5
14	3,5	34883-41-5
15	4,4'	2050-68-2
Trichlorobiphenyls		
16	2,2',3	38444-78-9
17	2,2',4	37680-66-3
18	2,2',5	37680-65-2
19	2,2',6	38444-73-4
20	2,3,3'	38444-84-7
21	2,3,4	55702-46-0
Trichlorobiphenyls (cont.)		
22	2,3,4'	38444-85-8
23	2,3,5	55720-44-0
24	2,3,6	55702-45-9
25	2,3',4	55712-37-3
26	2,3',5	38444-81-4
27	2,3',6	38444-76-7
28	2,4,4'	7012-37-5
29	2,4,5	15862-07-4
30	2,4,6	35693-92-6
31	2,4',5	16606-02-3
32	2,4',6	38444-77-8
33	2',3,4	38444-86-9
34	2',3,5	76708-77-5
35	3,3',4	55712-37-3
36	3,3',5	38444-87-0
37	3,4,4'	38444-90-5
38	3,4,5	53555-66-1
39	3,4',5	38444-88-1
Tetrachlorobiphenyls		
40	2,2',3,3'	38444-93-8
41	2,2',3,4	52663-59-9
42	2,2',3,4'	36559-22-5
43	2,2',3,5	70362-46-8
44	2,2',3,5'	41464-39-5
45	2,2',3,6	70362-45-7

TABLE II-1 (cont.)

No.*	Structure	CAS No.	No.*	Structure	CAS No.
Pentachlorobiphenyls (cont.)				Hexachlorobiphenyls	
99	2,2',4,4',5	38380-01-7	128	2,2',3,3',4,4'	38380-07-3
100	2,2',4,4',6	39485-83-1	129	2,2',3,3',4,5	55215-18-4
101	2,2',4,5,5'	37680-73-2	130	2,2',3,3',4,5'	52663-66-8
102	2,2',4,5,6'	68194-06-9	131	2,2',3,3',4,6	61798-70-7
103	2,2',4,5',6	60145-21-3	132	2,2',3,3',4,6'	38380-05-1
104	2,2',4,6,6'	56558-16-8	133	2,2',3,3',5,5'	35694-04-3
105	2,3,3',4,4'	32598-14-4	134	2,2',3,3',5,6	52704-70-8
106	2,3,3',4,5	70424-69-0	135	2,2',3,3',5,6'	52744-13-5
107	2,3,3',4',5	70424-68-9	136	2,2',3,3',6,6'	38411-22-2
108	2,3,3',4,5'	70362-41-3	137	2,2',3,4,4',5	35694-06-5
109	2,3,3',4,6	74472-35-8	138	2,2',3,4,4',5'	35065-28-2
110	2,3,3',4',6	38300-03-9	139	2,2',3,4,4',6	56030-56-9
111	2,3,3',5,5'	39635-32-0	140	2,2',3,4,4',6'	59291-64-4
112	2,3,3',5,6	74472-36-9	141	2,2',3,4,5,5'	52712-04-6
113	2,3,3',5',6	68194-10-5	142	2,2',3,4,5,6	41411-61-4
114	2,3,4,4',5	74472-37-0	143	2,2',3,4,5,6'	68194-15-0
115	2,3,4,4',6	74472-38-1	144	2,2',3,4,5',6	68194-14-9
116	2,3,4,5,6	18259-05-7	145	2,2',3,4,6,6'	74472-40-5
117	2,3,4',5,6	68194-11-6	146	2,2',3,4',5,5'	51908-16-8
118	2,3',4,4',5	31508-00-6	147	2,2',3,4',5,6	68194-13-8
119	2,3',4,4',6	56558-17-9	148	2,2',3,4',5,6'	74472-41-6
120	2,3',4,5,5'	68194-12-7	149	2,2',3,4',5',6	38380-04-0
121	2,3',4,5',6	56558-18-0	150	2,2',3,4',6,6'	68194-08-1
122	2',3,3',4,5	76842-07-4	151	2,2',3,5,5',6	52663-63-5
123	2',3,4,4',5	65510-44-3	152	2,2',3,5,6,6'	68194-09-2
124	2',3,4,5,5'	70424-70-3	153	2,2',4,4',5,5'	35065-27-1
125	2',3,4,5,6'	74472-39-2	154	2,2',4,4',5,6'	60145-22-4
126	3,3',4,4',5	57465-28-8	155	2,2',4,4',6,6'	33979-03-2
127	3,3',4,5,5'	39635-33-1	156	2,3,3',4,4',5	38380-08-4

TABLE II-1 (cont.)

No.*	Structure	CAS No.	No.*	Structure	CAS No.
Nonachlorobiphenyls				Decachlorobiphenyl	
206	2,2',3,3',4,4',5,5',6	40186-72-9	209	2,2,3,3',4,4'5,5',6,6'	2051-24-3
207	2,2',3,3',4,4',5,6,6'	52663-79-3			
208	2,2',3,3',4,5,5',6,6'	5121-88-0			

*Ballschmiter Number (Ballschmiter and Zell, 1980)

TABLE II-2

CAS and RTECS Numbers for Some Aroclors*

Aroclor No.	CAS No.	RTECS No.	Reference
1016	12674-11-2	NA	NIOSH, 1983
1221	11104-28-2	TQ 1352000	NIOSH, 1983
1232	11141-16-5	TQ 1354000	NIOSH, 1983
1242	53469-21-9	TQ 1356000	NIOSH, 1983
1248	12672-29-6	TQ 1358000	NIOSH, 1983
1254	11097-69-1	TQ 1360000	NIOSH, 1983
1260	11096-82-5	TQ 1362000	NIOSH, 1983
1262	37324-23-5	NA	Alford-Stevens et al., 1986a
1268	11100-14-4	NA	Alford-Stevens et al., 1986a

NA = Not available

TABLE II-3 (cont.)

Substrate	PCDF Content (ppm)					Reference
	Tri-	Tetra-	Penta-	Hexa-	Total	
Phenoclor DP-6	0.2	2.1	2.6	5.6	11	Morita et al., 1977a
Phenoclor DP-6	--	0.7	10	2.9	14	Bowes et al., 1975
Aroclor T-1200	--	0.1	0.4	0.5	1.0	Bowes et al., 1975
Aroclor T-1241	--	2.4	2.7	0.8	5.9	Morita et al., 1977a
Aroclor T-1242	--	2.3	2.3	--	4.5	Morita et al., 1977a
Aroclor T-1248	--	0.5	2.3	--	2.8	Morita et al., 1977a
Aroclor T-1248[c]	0.3	5.8	5.6	0.7	12	Morita et al., 1977a
Aroclor T-1254	--	0.1	0.2	1.4	1.7	Bowes et al., 1975
Aroclor T-1254	--	0.2	0.4	0.9	1.5	Bowes et al., 1975
Aroclor T-1254	--	0.1	3.6	1.9	5.6	Morita et al., 1977a
Aroclor T-1260	--	0.2	0.3	0.3	0.8	Bowes et al., 1975
Aroclor T-1260	--	0.8	0.9	0.5	2.2	Morita et al., 1977a
Aroclor T-1264	--	4.8	9.4	2.0	16	Morita et al., 1977a
Clophen A-30	1.6	2.3	1.0	--	4.9	Morita et al., 1977a
Clophen A-40	1.5	5.4	6.9	--	14	Morita et al., 1977a
Clophen A-50	0.7	8.3	4.1	1.8	15	Morita et al., 1977a
Clophen A-60	--	1.4	5.0	2.2	8.4	Bowes et al., 1975

[a]No data found for hepta-

[b]Yu-Cheng oil also contained 22-113 ppm PCBs and 9-38 ppm PCQs. Kanemi oil also contained 151-968 ppm PCBs and 490-866 ppm PCQs. Kanechlor 400 also contained 999,800 ppm PCBs and 209 ppm PCQs. Used Kanechlor 400 also contained 961,900-999,000 ppm PCBs and 690-31,000 ppm PCQs.

[c]Used PCB

I. SUMMARY

Evaluation of the health effects of polychlorinated biphenyls (PCBs) in the environment represents a highly complex problem. The empirical formula for PCBs is $C_{12}H_{10-n}Cl_n$ (n=1-10), which in theory allows for the formation of 209 different individual PCBs. Commercial formulations of PCBs enter the environment as mixtures consisting of a variety of individual PCB congeners and impurities, including polychlorinated dibenzofurans (PCDFs). The toxicity of some individual PCB congeners and specific impurities such as the PCDFs has been examined using laboratory animals.

Various commercial mixtures of PCBs have been marketed under a number of trade names including Aroclor (Britain and USA), Phenochlor or Pyralene (France), Clophen (FRG), Kanechlor or Santotheam (Japan), Fenclor (Italy) and Sovol (USSR). Since commercial formulations contain a complex mixture of PCBs, the physical properties of a given formulation will vary depending on the components and composition of the mixture. The physical properties of the biphenyl family vary considerably, having a molecular weight range of 154 for biphenyl to 499 for decachlorobiphenyl (the PCB with the most chlorines), a log octanol/water partition coefficient range of 3.76-8.26 for PCBs, and an aqueous solubility range of 9.77×10^{-10} to 4.68×10^{-5} mol/ℓ.

Commercial PCB mixtures are estimated to volatilize from ambient water, with half-lives ranging from 2 months to >150 years for low and high molecular weight mixtures, respectively. The most important input parameter affecting volatilization rates is the octanol/water partition coefficient, since this reflects the amount of PCBs partitioning into the water from sediments and biota, and the amount available for volatilization. Sediments waste sites containing PCBs. In all cases, total PCB levels are best characterized by specific congener analysis or total PCB by perchlorination rather than in terms of Aroclors, because the congener patterns in environmental media and biological tissues usually do not match those in Aroclor fluids unless massive contamination has occurred (typical of spills and some occupational situations). Thus, predictive models based on specific congener data must also be utilized.

The less chlorinated congeners predominate in air samples from known contaminated areas, and in water and wet deposition samples with the temperature and amount of sediment in river and water samples being important co-variables. In contrast, the more highly chlorinated isomers with substituents at the 2,4,5- or 2',4',5'-positions tend to bioaccumulate in some crop vegetables, game animals, fish and in human tissue samples. PCBs in contaminated soils can be absorbed by plants and vegetables with shallow-root systems, although volatilization in this situation is also favored; erosion of such particles will also cause contamination of sediments. The more chlorinated congeners will dominate in soils and sediments and the resident biota (cash crops, vegetables, fish, aquatic life). The absolute levels in any situation depend on which of the competing processes dominates as estimated in Table IV-7. Congeners of Aroclor 1016 have been detected in finished drinking water obtained from the Hudson River and samples from well water taken during the National Organic Monitoring Survey. The finished drinking water from Dority Reservoir treatment and distribution in upstate New York was reported to contain Aroclor 1016. Water from the public water supply system of the village of Fort Edward, located near the township of Moreau of Saratoga County, New York is obtained from Dority Reservoir treatment and distribution system. The level of Aroclor 1016 in this finished

Although phenolic products are the major PCB metabolites, sulfur-containing metabolites, trans-dihydrodiols, polyhydroxylated PCBs and their methyl ether derivatives have been identified. The presence of trans-dihydrodiol metabolites strongly suggests metabolism through an arene oxide intermediate. Arene oxides have been implicated in cellular necrosis, mutagenicity and carcinogenicity; however, the role of metabolism in the genotoxicity of PCBs has not been delineated.

Studies using laboratory animals clearly demonstrate that PCBs can cross the placental barrier and accumulate in the fetus. Another major route of exposure occurs by lactation in which the highly lipophilic PCBs are readily transferred from maternal milk to the neonate. The latter route represents the most important route of PCB exposure for the young.

Preferential structure-dependent bioaccumulation of PCB congeners has been observed in human liver, adipose tissue, serum and milk. 2,2',4,4',5,5'-hexa-CB, 2,2',3,4,4',5'-hexa-CB, 2,2',3,3',4,4',5-hepta-CB and 2,2',3,4,4',5,5'-hepta-CB are major components of both a high molecular weight commercial mixture (Aroclor 1260) and human milk. On the other hand, 2,4,4'-tri-CB, 2,4,4',5-tetra-CB, 2,2',4,4',5-penta-CB, 2,3',4,4',5-penta-CB and 2,3,3',4,4',5-hexa-CB are identified as major components of human milk extract, while representing only minor components of Aroclor 1260. Human studies also clearly indicate the importance of lactation as the major route of infant PCB exposure, and represent a major route of depuration for mothers with high body burden of PCBs.

In evaluating the health effects of PCBs in animals, it is important to consider the isomer specific composition of the PCBs and potential impurifor 4 days (1 mg/kg bw/day). Hepatomegaly results from liver cell hypertrophy, which is caused by fatty infiltration and proliferation of the smooth endoplasmic reticulum. The latter response is associated with the induction of certain hepatic enzymes, particularly the microsomal mixed function oxidases. Hepatic fluorescence, which is suggestive of porphyria has also been reported after exposure of rats for 16 weeks to 10 ppm of Aroclor 1254 (0.5 mg/kg bw/day). Focal necrosis and iron-containing deposits in Kuppfer cells have been observed at higher levels of exposure.

PCBs have also been shown to produce immunosuppression, which maybe associated with thymic atrophy, lymphocytopenia and splenomegaly. Other PCB-related toxicity include a reduction in food and water intake, reduced rate of body weight gain (wasting syndrome), and decreased body temperature. Another sensitive indicator of PCB exposure is an enlarged thyroid. Ultrastructural evidence suggestive of increased thyroid gland activity has been reported in rats maintained on diets containing as little as 5 ppm Aroclor 1254 (0.25 mg/kg bw/day) for 4 weeks.

In a chronic study that defined a NOAEL, BALB/CJ mice were maintained for 9 months on diets containing 0, 3.75, 37.5 or 375 ppm of the Aroclors 1221, 1242 or 1254 (0.45, 4.57 or 45.7 mg/kg bw/day). The Aroclor with the lowest chlorine content (1221) produced no liver lesions, while exposure to Aroclor 1242 resulted in increased liver weight in the high-dose group. In mice exposed to Aroclor 1254, increased mortality was observed in the high-dose group, mild hepatopathology observed in the median-dose group, and no liver lesions detected in the low-dose group. The NOEL observed in the study using mice of 0.45 mg/kg bw/day is nearly identical to the LOELs of mink. Adult monkeys exposed to Aroclor 1016 in the diet did not have any clinical growth or reproductive abnormalities. However, infants born to the 1 ppm Aroclor 1016 group (0.042 mg/kg bw/day, assuming a monkey consumes 4.2% of its body weight/day) were significantly smaller than controls. Thus, 0.25 ppm (0.0105 mg/kg bw/day) appears to be a NOAEL for chronic oral exposure to Aroclor 1016 in rhesus monkeys.

Reports of mutagenicity in the Ames assay are conflicting. Most reports indicate a lack of mutagenicity. No report of cytogenetic changes or dominant lethal effects attributable to PCBs have been located in the available literature.

Human exposure to PCBs may come from contact with industrial products, accidental contamination of foodstuffs or from association with contaminated environmental components. Similar signs of toxicity are associated with oral, inhalation or dermal exposure. Chloracne is the most commonly encountered dermatologic symptom. These lesions comprise follicular keratosis with comedone formation and acneform eruptions. Other reported dermatologic symptoms include rash, burning sensation, pigmentation (darkening), thickening, and discoloration of the fingernails. It is not clear whether PCB mixtures are solely responsible for chloracne or whether contamination of PCBs with polychlorinated dibenzofurans (PCDFs) resulted in chloracne and other adverse health effects. In Yusho and Yu-cheng poisoning incidents, the presence of PCDFs in the PCB contaminated rice oil and in the liver and other tissues of the victims indicates that PCDFs were the responsible toxic compounds. Hepatic effects associated with PCB exposure include hepatomegaly, hepatic enzyme induction with accelerated rate of drug metabolism, and hepatic dysfunction indicated by an increase in serum hepatic enzyme

PCBs (Aroclor 1260, Kanechlor 500, Aroclor 1254, Clophen A-30 and Clophen A-60) have been evaluated for carcinogenicity in several animal bioassays. Aroclor 1260 induced a statistically significant increase of heptocellular carcinomas in two rat (Sherman, Sprague-Dawley) feeding studies. Kanechlor 500 produced a statistically significant liver tumor response in dd mice when given in the diet for 32 weeks. Aroclor 1254 fed in the diet to mice (Balb/cj) and rats (Fischer 344) induced increased incidences of liver tumors, and while the incidences are dose-related they were not statistically significant. Clophen A-30 and A-60 induced hepatocellular carcinomas in rats after 832 days of feeding 100 ppm in the diet. This level of carcinogenic evidence in rats and mice for some commercial PCBs (Aroclor 1260, Kanechlor 500 and Aroclor 1254, Clophen A-30 and Clophen A-60) constitute sufficient evidence for carcinogenicity of these commercial PCBs in animals using weight of evidence criteria in the U.S. EPA's guidelines for carcinogen risk assessment (U.S. EPA, 1986a). Only one recent epidemiologic study reports the presence of a carcinogenic risk of liver cancer to humans by ingestion. A significant risk of liver cancer was observed among victims of the Yusho accident in Japan, which involved exposure to contaminated rice oil. There is some uncertainty regarding concurrent exposure to other possibly carcinogenic substances. The authors of the study have not derived conclusions regarding the relationship of exposure to PCB-contaminated rice oil and increased cancer risk. At present, the human epidemiologic evidence is suggestive, but from a weight of evidence classification of the data must be currently regarded as inadequate because of the tentative nature of the data. The authors of these studies have urged caution in the interpretation of their results.

TABLE II-4 (cont.)

Formulation	PCDF Levels (ppm)		Total	Percentages of Total PCDFs for These Two Derivatives
	2,3,7,8-[b,c] TCDF	2,3,4,7,8-[b,d] PeCDF		
Clophen[b]				
A-30	1.0	0.1	4.9	22
A-40	2.1	0.7	14	20
A-50	3.6	0.6	15	28

[a]Masuda et al., 1982

[b]Calculated from Morita et al., 1977a

[c]Based on GC retention time, but subsequently confirmed by Buser et al. (1978). This was subsequently found to include also the 2,3,4,8-TCDF.

[d]The order of elution obtained by Buser et al. (1978) is assumed to pertain to the GC column utilized.

[e]Used PCB

-- Below detection limit

TABLE II-6

Some Physical Properties of Aroclors[a,b,c]

Property	VALUE 1016	1221	1232	1242	1248	1254	1260
Appearance	clear oil	clear oil	clear oil	clear oil	clear oil	light yellow viscous liquid	light yellow sticky resin
Chlorine (percent)	41	20.5-21.5	31.4-31.5	42	48	54	60
Density (g/mℓ) (25°C)	1.33	1.15	1.24	1.35	1.41	1.50	1.58
Distillation range (°C)	325-356	275-320	290-325	325-366	340-375	365-390	385-420
Evaporation loss % at 100°C/6 hours		1-1.5	1-1.5	0-0.4	0-0.3	0-0.2	0-0.1
Aqueous solubility (mg/ℓ)	0.42[d]	0.59[e]	NA	0.24,0.34[d] 0.13[c]	0.054	0.012, 0.024[f] 0.056[g]	0.027
Lipid solubility (organic solvents)	very soluble	very soluble	very soluble	very soluble	very soluble	very soluble	very soluble
Vapor pressure (mm Hg at 25°C)	[4×10^{-4}]	[6.7×10^{-3}]	[4.06×10^{-3}]	4.06×10^{-4}	4.94×10^{-4}	7.71×10^{-5}	4.05×10^{-5}
Log octanol/water partition coefficient	4.38[d] >5.58[i,j]	[2.8] 4.09[j,k]	[3.2] >4.54[j,k]	4.11[d] >5.58[i,j]	[5.75][h] >6.11[i,j]	[6.03][h]	[7.14][h] >6.11[i,j]
Adsorption capacity of activated carbon (mg/g)	NA	242[l]	630[l]	NA	NA	NA	NA
Conversion factors 1 ppm = 1 mg/m³ =	10.05 mg/m³ 0.0948 ppm	8.21 mg/m³ 0.122 ppm	9.50 mg/m³ 0.105 ppm	10.9 mg/m³ 0.0917 ppm	12.2 mg/m³ 0.0816 ppm	13.4 mg/m³ 0.0745 ppm	15.4 mg/m³ 0.0651 ppm

[a]Adapted from Callahan et al., 1979
[b]All values not superscripted are from Monsanto, 1974.
[c]Bracketed data are estimated.
[d]Paris et al., 1978
[e]Hollifield, 1979
[f]Dexter and Pavlov, 1978
[g]Haque et al., 1974
[h]Hansch et al., 1974; Chiou et al., 1977
[i]Chiou et al., 1977
[j]Partition coefficient of lowest chlorinated biphenyl present in significant quantities.
[k]Tulp and Hutzinger, 1978a
[l]Ramanathan, 1984
NA = Not available

depend on molecular weight but do for ortho-substituted PCBs (Burkhard et al., 1985b; Arbuckle, 1986). Vapor-particle partitioning of PCBs depends markedly on temperature (Bidleman et al. 1986); at 20°C, only 2.1% of Aroclor 1254 was retained on a filter, whereas at 0°C the percentage was 25%. Differential volatilization of the less chlorinated components of Aroclor 1254 has been observed during air sampling with Tenax-GC, XAD-2 resin, and deactivated Florisil (Brownlow and Que Hee, 1985; Lin and Que Hee, 1987). Enrichment in the higher chlorinated congeners is observed also in the residue after volatilization of the less chlorinated compounds (Lin and Que Hee, 1987).

Individual PCB congeners increase in water solubility, with decreasing chlorination and increasing temperature (Yalkowsky et al., 1983; Mackay et al., 1980; Dickhut et al., 1986). Beyond the Cl_4-PCBs, most of the PCBs tend to be relatively insoluble (Dickhut et al., 1986); for example, 3,3',4,4'-Cl_4-PCB has a solubility of (1.95×10^{-9}) M at 25°C; decachlorobiphenyl similarly has a solubility of (1.30×10^{-12}) M. Octanol/water coefficients increase with increasing chlorination (Rapaport and Eisenreich, 1984). Miller et al. (1985) showed that log K_{ow} values at 25°C varied between 3.76 (biphenyl) and 8.26 for decachlorobiphenyl. The Cl_4-PCBs had a log K_{ow} of ~5.7; the Cl_5-PCBs of ~6.0, and the Cl_6-PCBs of ~7.0. In all of these systems the chlorine substitution in an isomeric class also influences physical property.

PCBs are aromatic and hence can be detected with great sensitivity using ultraviolet (UV) detectors (λ_{max} are at 197-222, 214-265 and 267-302 nm for PCBs), and give strong molecular ions in mass spectra, but because of the most commonly used technique (Alford-Stevens et al., 1986a,b; Gebhart et al., 1985; Silven et al., 1985). However, it is 2-3 orders of magnitude less sensitive than the electron capture detector. Electron impact (70eV) fragmentation is recommended as the basis of U.S. EPA method 680 (Alford-Stevens et al., 1986b). It was shown that the mass spectrometric response factors within an isomeric class varied between 1.3 and 4.6 (Gebhart et al., 1985). Nevertheless, nine surrogate congeners can represent all PCBs in mass spectroscopic response; therefore, the recommendation is that detection limits be found in terms of these nine surrogates.. The nine surrogates in terms of chlorine substitution are as follows: 2-, 2,3-, 2,4,5-, 2,2',4,6-, 2,2',3,4,5'-, 2,2',4,4',5,6'-, 2,2',3,4',5,6,6'-, 2,2',3,3',4,5',6,6'- and decachlorobiphenyl (for Cl_9 and Cl_{10}). The only isotopically labeled PCB available is 3,3',4,4'-Cl_4 PCB-d_6 (Gebhart et al., 1985). The recovery of Aroclors from waters shows a negative bias between 15 and 27% when analysed as Aroclors, thus necessitating specific congener analysis (Alford-Stevens et al., 1986b).

Positive methane chemical ionization-GC/MS of PCBs has been reported by Voyksner et al. (1986). The $(M+H)^+$ and $(M+H_2-Cl)^+$ ions were monitored. The relative response for all congeners varies between 0.14 and 1.79 (compare electron impact range of 0.22-4.08), and was generally 2-6 times more sensitive than electron impact detection (but still not as sensitive as electron capture detection).

Environmental samples often require many clean-up steps before interfering peaks can be removed. For example, sediments require Soxhlet extraction or ultrasonic homogenization in hexane/acetone or isopropanol/dichloroescence detector with excitation at 340 nm has also been used after a 37-50 μBondapak/Corasil column or a μBondapak C_{18} column (Miller et al., 1985).

Two dimensional TLC using a hexane/ethyl acetate mobile phase and silica gel plates has been reported (Lay et al., 1976); the fluorescence characteristics of PCBs in α-cyclodextrin using room temperature phosphorescence can discriminate some individual PCB congeners (Femla et al., 1985).

Other analytical methods of some use are perchlorination (Lin and Que Hee, 1985) and dechlorination (Seymour et al., 1986). Perchlorination has been used extensively, especially for Yusho samples (Miyata et al., 1985; Kashimoto et al., 1985).

Chemical Reactions

Pyrolysis. A route with environmental implications is the thermal production of PCDFs from PCBs. Buser et al. (1978) and Buser and Rappe (1979) showed that when specific PCBs were pyrolyzed in quartz ampules between 500 and 700°C, PCDF yields in the 1-10% range could be obtained, though they were accompanied by many other products including chlorinated benzenes, naphthalenes and hydroxy PCBs. Buser et al. (1978) described the products of pyrolysis at 600°C identified by GC/MS. There appear to be four major paths for production of PCDFs from PCBs: loss of two ortho chlorines, loss of ortho hydrogen as well as chlorine, loss of an ortho hydrogen as well as chlorine but involving a shift of chlorine from the 2- to the 3-position and loss of two ortho hydrogens. These paths are summarized in

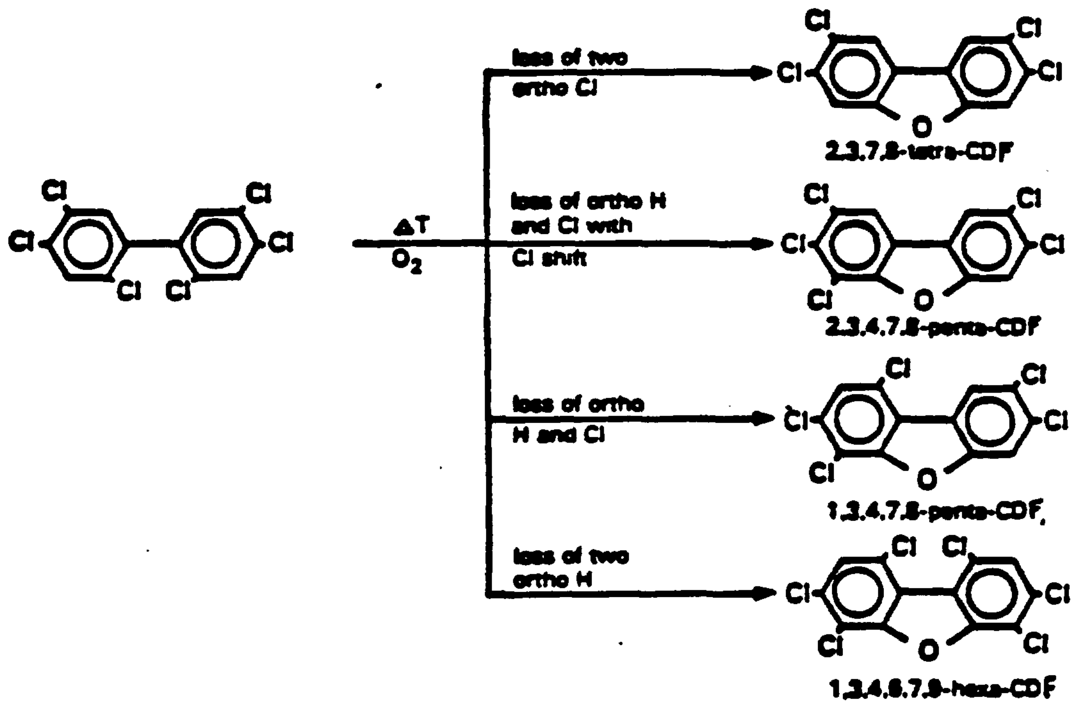


FIGURE II-1

Possible Reaction Schemes to Produce PCDFs from the Pyrolysis of 2,2', 4,4', 5,5'-Hexachlorobiphenyl

Source: Adapted from Buser and Rappe, 1979 volatilization and solubilization (Hutzinger et al., 1974), although sedimentation removal also occurs. Higher molecular weight PCBs will principally adsorb to sediments and biota, although some volatilization (Hutzinger et al., 1974) may occur.

Photodecomposition. PCBs in water at sunlight wavelengths can be photochemically degraded (Crosby and Moilanen, 1973), resulting in reductive or hydroxylative dechlorination as well as dibenzofurans. The hydroxylated products can also form dibenzofurans on boiling or at high pH. Reductive dechlorination occurs in organic solvents at 300 nm; the chlorines next to the biphenyl bridge are cleaved preferentially (Hutzinger et al., 1974).

PCBs in water can be photolyzed (Crosby and Moilanen, 1973; Hutzinger et al., 1974; Pomerantz et al., 1978; Callahan et al., 1979). Hydroxylative dechlorination can also occur as well as reductive dechlorination (Crosby and Moilanen, 1973; Hutzinger et al., 1974). The rate and extent of PCB photodegradation by sunlight are extremely difficult to assess in the environment. Complicating factors include the diversity of environmental conditions and the propensity of PCBs (particularly the more photolabile highly-chlorinated biphenyls) to adsorb to sediments and organic materials (Hutzinger et al., 1974). Hutzinger (1972) observed 0.2% 2-PCDF production after 7 days of ultraviolet irradiation (310 nm) of aqueous solutions of 2,5,2'5'-tetrachloro- and 2,5-dichlorobiphenyls (5 mg/ℓ). These products were confirmed by Crosby and Moilanen (1973). However, Hutzinger (1972) found no PCDFs after some aqueous PCB samples (167 mg/ℓ) had been exposed to sunlight for >2 months. This discrepancy may have arisen because of the different irradiation times and different wavelengths used. The yield of

Modeling is complicated by the numerous contradictory solubilities, octanol/water partition coefficients, and Henry's Law constants for each Aroclor (Callahan et al., 1979; Doskey and Andren, 1981; Mabey et al., 1981; Burkhard et al., 1985c; Mackay et al., 1986). This arises because Aroclors are mixtures. Thus, some Henry's Law constants varied over 4 orders of magnitude for the same Aroclor (Doskey and Andren, 1981). The volatilization half-lives for various Aroclors calculated, based on a number of input values for these parameters (Burns et al., 1981), appear to be in the following ranges: Aroclor 1221 and Aroclor 1232, 2 months to 1 year; Aroclor 1016, <2-7 years; Aroclor 1242, 2-7 years; Aroclor 1248, 3-8 years; Aroclor 1254, >4-11 years; Aroclor 1260, >60 to >150 years. However, exact data can only be obtained by consideration of specific congeners.

One of the major controlling factors found to determine the volatilization half-life (Burns et al., 1981) was the octanol/water partition coefficient, since this is inversely related to the amount of PCBs partitioning into the water from sediments and biota and the level available for volatilization. This applies for laboratory as well as environmental conditions. Again, as expected of mixtures, several laboratory values for the octanol/water partition coefficient varying over 2 orders of magnitude were found for the Aroclors (Callahan et al., 1979; Garten and Trabalka, 1983; Miller et al., 1985). The advantage of using the Burns et al. (1981) approach is that adsorption is also taken into account when calculating volatilization half-lives, while models for volatilization alone do not consider adsorption or do so indirectly (Mackay and Leinonen, 1975). The reduction of volatilization half-lives in the presence of adsorption has been studied in the laboratory. Oloffs et al. (1972, 1973) showed that

Exchange Between Media

Air/water exchange of PCBs has been modeled by Mackay et al. (1986). The example has been provided of a Cl_5-PCB in the Great Lakes Basin. This PCB air concentration is 5.7% sorbed and 94.3% in gaseous form at 15°C; in the water, 19.7% is sorbed and 80.3% is dissolved. While there is a net volatilization effect, this is countered (25%) by wet and dry deposition. On the average, rainfall contains 68.2 ng PCB/ℓ, mostly all associated with washed out particles. Lower temperatures will enhance adsorption and sorption. Higher temperatures will enhance volatilization and solubilization. Thus, a complex cycling of a PCB in an ecosystem is expected. Burkhard et al. (1985c) have noted that the relative proportions of the PCBs in environmental mixtures and Aroclors are different. They also modeled how specific Cl_4, Cl_5 and Cl_6 PCB congeners would be depleted or enriched in a 3-phase system (water/air/suspended particulate matter). The binding of 2,2',5,5'-tetrachlorobiphenyl to dissolved humic acid was studied by Hassett and Millicic (1985), using an aspiration method. The equilibrium binding constant is 7.1×10^4. The rate constant for release of bound PCB congener by humic acid is 3.5×10^{-3} min^{-1}; the rate constant for binding of dissolved PCB congener by humic acid is 1.7×10^{-4} ℓ (mg dissolved organic carbon)$^{-1}$ min^{-1}.

Biodegradability

A number of investigators have reported on biodegradability and its mechanism for PCBs (Hutzinger et al., 1972, 1974; Kaiser and Wong, 1974; Branson et al., 1975; Berlin et al., 1975; Wong and Kaiser, 1976; Furukawa et al., 1978, 1983; Tabak et al., 1981a,b). Biodegradability is generally related to the number of hydrogens available. These positions appear to be range of 3.76-8.26, and a solubility range of 9.77×10^{-10} to 4.68×10^{-5} moles/ℓ (moles/ℓ x molecular weight x 10^6/ℓ = μg/ℓ) (Yalkowsky et al. 1983).

PCBs will volatilize from ambient waters with half-lives ranging between 2 months and >150 years (Burns et al., 1981; Doskey and Andren, 1981; Callahan et al., 1979; Mabey et al., 1981). The most important parameter affecting volatilization rates was found to be the octanol/water partition coefficient, showing that the partitioning of the PCBs from the sediments and biota into the water was the limiting factor affecting volatilization.

Adsorption appears to be the dominant removal mechanism for highly chlorinated PCBs. Using the input parameters from the previously mentioned sources, sorption to sediment effectively binds between 45 and >99% of the PCBs present in water depending on the PCB and the organic matter present in the sediment. The higher the organic matter in the sediment or the higher the chlorination, the more strongly sorbed will be the PCB. PCBs have been demonstrated to undergo complete cycling in ecosystems.

As for volatilization and sorption, biodegradation is also a significant removal mechanism for the less chlorinated species (Callahan et al., 1979; Hutzinger et al., 1972, 1974; Kaiser and Wong, 1974; Tabak et al., 1981a,b). Based on published reports, PCBs containing ≤3 chlorines tend to be degraded in the environment, although estimation of half-lives is very difficult given the great variability in the reported literature. PCBs with four chlorines appear to be somewhat less degradable. PCBs with five or more chlorines appear to be recalcitrant.

TABLE III-1

Quantitative and Qualitative Analysis of PCBs in Aroclor 1260 and a Human Breast Milk Extract[a]

Congener Name[b]	Percentage in Aroclor 1260	Percentage in Human Milk[c]	Congener Name[b]	Percentage in Aroclor 1260	Percentage in Human Milk[c]
PCB-018	0.12	ND	PCB-118	0.49	6.5
PCB-017	0.05	ND	PCB-134	0.35	ND
PCB-024	0.01	ND	PCB-114	ND	0.33
PCB-016	0.04	ND	PCB-131	0.07	ND
PCB-029	0.02	ND	PCB-122	0.12	0.53
PCB-026	0.02	ND	PCB-146	1.3	1.9
PCB-028	0.04	8.8	PCB-153	9.6	12
PCB-021	0.01	ND	PCB-141	2.5	0.29
PCB-033	0.09	2.2	PCB-176	0.33	ND
PCB-053	0.04	ND	PCB-137	0.22	0.87
PCB-022	0.01	0.65	PCB-130	ND	0.59
PCB-045	0.07	ND	PCB-138	6.5	10
PCB-046	0.02	0.25	PCB-158	0.70	0.55
PCB-052	0.25	1.9	PCB-129	0.20	ND
PCB-043	0.02	ND	PCB-178	1.2	ND
PCB-049	0.06	0.66	PCB-175	0.49	ND
PCB-048	0.29	0.37	PCB-187	4.5	1.5
PCB-044	0.11	0.78	PCB-183	2.3	1.4
PCB-037	0.04	2.9	PCB-128	0.47	0.33
PCB-042	0.04	ND	PCB-167	0.16	0.85
PCB-041	0.25	1.3	PCB-185	4.1	0.11
PCB-040	0.03	ND	PCB-174	5.5	0.39
PCB-100	0.02	ND	PCB-177	1.9	0.61
PCB-074	0.03	11	PCB-171+202	1.2	0.37
PCB-070+076	0.15	0.61	PCB-156	0.45	4.87
PCB-095	2.7	ND	PCB-173	0.06	ND
PCB-091	0.07	ND	PCB-200	0.78	ND

contrast, the gas chromatogram of a composite human milk sample does not resemble the pattern of any commercial PCB, and pattern matching methods would not yield meaningful quantitative results. However, the high-resolution isomer-specific GC approach permitted quantitation of all the individual PCB components present in this mixture. Several PCB congeners, including 2,2',4,4',5,5'-hexa-CB, 2,2',3,4,4',5'- hexa-CB, 2,2',3,3',4,4',5-hepta-CB and 2,2',3,4,4',5,5'-hepta-CB are major components of both Aroclor 1260 and the human milk extract.

Another major PCB present in the human milk extract, (4.87%), (2,3,3',4,4',5-hexa-CB) is a minor component of Aroclor 1260 and other commercial PCBs (Ballschmiter and Zell, 1980; Jensen and Sundstrom, 1974) and has previously been identified as a major PCB contaminant of Japanese human milk extracts (Safe, 1982). The four remaining major PCB congeners identified in the human milk extract (2,4,4'-tri-CB, 2,4,4',5-tetra-CB, 2,2',4,4',5-penta-CB and 2,3',4,4',5-penta-CB) are minor components of Aroclor 1260 (<0.49% for all four isomers). It is likely that these penta- and tri-PCB congeners are derived from the lower chlorinated PCB formulations; however, it is noteworthy that with the exception of 2,4,4'-tri-CB, all of these compounds also contain 2,4,5-trichloro-substitution on one of the phenyl rings and a p-chloro group on the second phenyl ring. This high-resolution analytical study has also identified 2,4,4'-tri-CB as a major PCB component and confirms a previous report that identified this compound in a Japanese human milk extract (Yakushiji et al., 1979). The reasons for the persistence of this congener are not apparent. It was also of interest to note that several other compounds including 2,2',3,5',6-penta-CB (2.7%), 2,2',3,4',5',6-hexa-CB (7.4%), 2,2',3,3',4,5,5'-hepta-CB (5.5%) and governed absorption efficiencies was the degree of chlorination, since there was an increase in absorption of PCBs with increasing ring chlorination and molecular size. It is also conceivable that other structural factors may also play an important role in PCB absorption. For example, ortho-chlorine substitution decreases PCB ring coplanarity and there is evidence in both fish and rats that there may be decreased absorption of isomers with increasing ortho-chloro substituents (Tulp and Hutzinger, 1978a,b; Sparling and Safe, 1980b; Shaw and Cornell, 1980). Several rodent and monkey studies using either commercial PCB mixtures, reconstituted mixtures or individual compounds confirm that PCBs are readily absorbed from the GI tract and are distributed rapidly by the blood to diverse tissues. Liver and sometimes muscle act as major depots for PCB accumulation after initial exposure and absorption; these highly lipophilic compounds are then redistributed into adipose tissue and skin (Matthews and Dedrick, 1984). The effect of the vehicle on the GI absorption of PCBs has not been systematically evaluated.

Dermal. Several dermal studies with PCB congeners or mixtures demonstrate that these compounds are readily absorbed and elicit toxic or biologic effects at dermal and distal sites (Nishizumi, 1976; Miller, 1944; Puhvel et al., 1982; Wester et al., 1983). A recent study by Wester et al. (1983) reported the dermal absorption in guinea pigs and monkeys of synthetic ^{14}C-labeled PCBs containing 42 and 54% chlorine (by weight). Dermal absorption was estimated using the following relationship:

$$\%\ \text{Dose Absorbed} = \frac{\begin{array}{c}\text{total } ^{14}\text{C urinary excretion}\\ \text{following topical administration} \times 100\end{array}}{\begin{array}{c}\text{total } ^{14}\text{C urinary excretion}\\ \text{following parenteral administration}\end{array}}$$

association primarily with LDL; however, between 6 and 24 hours after administration the hexa-CB was redistributed from LDL to HDL and other protein-rich plasma fractions (Spindler-Vomachka et al., 1984). Recent studies using domestic animals have also demonstrated the importance of the lymphatic system as a transport route for PCBs (Ziprin et al., 1980, 1986), and this may contribute to the immunotoxic effects of PCBs.

The initial distribution of PCB mixtures and individual PCB congeners in diverse animal species is dependent on the structure(s) of the compounds and most importantly the biophysical factors that affect distribution of compounds in a multicompartment system (Matthews and Dedrick, 1984). Figure III-1 summarizes a flow diagram for the pharmacokinetics of PCBs in animals in which the initial distribution of serum containing PCBs is dependent on blood flow rates, blood volumes, PCB-blood serum absorption affinities, tissue/blood partition ratios, perfusion rates and tissue volumes (Matthews and Dedrick, 1984). In most animal species that have been investigated there is an initial uptake of PCBs into the liver and muscle which is due to high perfusion in the liver and the relatively large muscle volume. Subsequent redistribution of PCBs into adipose tissue and skin reflects the high affinity of the lipophilic PCBs for lipophilic tissues. At equilibrium the elimination of PCBs from all tissues will be dependent on the structure-dependent rates of metabolism of individual PCB congeners (see the Metabolism Section).

Several studies on the pharmacokinetics in rats and mice have been reported (Matthews and Dedrick, 1984; Schnellmann et al., 1985; Safe, 1980; Albro and Fishbein, 1972; Berlin et al., 1974; Matthews and Anderson, 1975;

Gage and Holm, 1976; Allen et al., 1974a,b; Tanabe et al., 1981; Sparling and Safe, 1980a,b; Matthews and Tuey, 1980; Lutz et al., 1977; Muhlebach and Bickel, 1981; Tuey and Matthews, 1977a,b, 1980; Morales et al., 1979; Morita and Oishi, 1977; Lucier et al., 1978; Clarke et al., 1984; Sugiura et al., 1975, 1976; Mizutani et al., 1977; Felt et al., 1977, 1979). Most of the reports using individual PCB congeners gave comparable results. Matthews and Anderson (1975) administered 0.6 mg/kg i.v. of the following ^{14}C-labeled PCB congeners to Sprague-Dawley rats: 4-CB (1-CB) 4,4'-di-CB (2-CB) 2,2',4,5,5'-penta-CB (5-CB) and 2,2',4,4',5,5'-hexa-CB (6-CB). Early time points illustrate the relatively high levels of all compounds in liver and muscle; the subsequent decrease of PCBs in these tissues was followed by preferential bioaccumulation of the PCB congeners in adipose tissue and skin. Lutz et al. (1977) proposed one model based on the pharmacokinetic data obtained for these isomers, the flow diagram illustrated in Figure III-1 and the known compartment sizes and perfusion rates from the experimental animal (Sprague-Dawley rat). This pharmacokinetic model has also been reviewed by Matthews and Dedrick (1984). The tissue/blood distribution ratio and kinetic parameters are summarized in Tables III-2 and III-3. The results illustrate a number of important points, namely:

1. The highly lipophilic parent compounds tend to preferentially bioconcentrate in lipophilic tissues (adipose tissue and skin) whereas the more polar metabolites are found in the hydrophilic cell tissues/compartments;

2. The magnitude of the metabolic clearance parameters (Km) are dependent on structure; the Km for the more rapidly metabolized CB-1 congener is 10.0 whereas these values decrease with increasing ring chlorination; the Km value for 2,2',4,4',5,5'-hexa-CB was <0.2% of the Km for 4-CB;

3. The mathematical model developed for PCB pharmacokinetics using the multicompartment system (see Figure III-1) can simulate and predict the behaviour of both parent compound and metabolite. For example, the mass balance equation for a tissue in which metabolism occurs (for example, liver, L) takes the form.

TABLE III-3

Pharmacokinetic Parameters for Individual PCB Congeners in the Rat*

Rate constant	1-CB	2-CB	5-CB	6-CB
Metabolic clearance, Km, mℓ/min	10.0	2.0	0.39	0.045
Kidney clearance, Kk, mℓ/min	0.20	0.133	0.033	0.030
Biliary clearance, KB, mℓ/min	0.20	0.35	0.30	0.30
Gut reabsorption, KG, min^{-1}	0.00016	0.00016	0.00016	0.00016
Fecal transport, KF, min^{-1}	0.0008	0.0008	0.0008	0.0008

*Source: Adapted from Lutz et al., 1977

1-CB:(4-CB)
2-CB:(4,4'-di-CB)
5-CB:(2,2',4,5,5'-penta-CB)
6-CB:(2,2',4,4',5,5'-hexa-CB)

TABLE III-4

Biological Half-Lives of Individual Chlorobiphenyls in Rats[a,b]

Peak No.	Type	Type A and Type B (I)			Type B (II) and Type C			Structure
		t_1 (day)	Duration[c] (day)	r	t_2 (day)	Duration[c] (day)	r	
11[d]								
21	A	0.15	0.13-0.5	0.94				2,2'
22[d]								2,5
23	A	0.34	0.12-0.5	0.86				2,4 2,3'
24	A	0.18	0.13-1	0.99				2,4'
25[e]								4,4'
31	A	0.11	0.13-0.25	1.00				2,2',6
32	A	0.18	0.13-1	0.98				2,2',5
33	A	0.21	0.13-1	0.92				2,2',4
34	A	0.21	0.12-1	0.99				2,2',3 2,3',6
35	A	0.23	0.13-1	0.99				2,4',6
36	A	0.32	0.13-1	0.97				2,3',5 2,3',5'
37	A	0.29	0.13-1	0.81				2,3',4
38	B	1.4	0.13-1	0.97	6.0	7-15	1.00	2,3,3' 2,4,4'
39	A	0.20	0.13-1	0.98				2,3',4'
310	A	0.34	0.13-1	0.99				3,4,4'
41	A	0.12	0.13-0.25	1.00				2,2',4,6
42	A	0.12	0.13-0.25	1.00				
43	B	0.89	0.13-3	0.72	3:4	3-15	1.00	2,2',5,5' 2,2',3,5
44								2,2'4,5 2,2',4,5
45	B	3.8	0.13-7	0.73	70	7-90	0.73	2,3,3',6 2,3',4,6 2,3',5',6
46								2,4,4',6 2',2,3,5' 2,3',4,6 2,2',4,4'
47	A	1.4	0.13-3	0.90				2,2',3,4'
48								2,2',3,3' 2,2',3,4
49	A	0.83	0.13-3	0.92				
410	B	3.1	0.13-7	0.93	37	7-45	0.98	2,3',4',5 2,4,4',5
411								2,3',4',5' 2,3,3',4
412	A	0.29	0.13-0.25	1.00				2,3,4,4'
413	B	2.4	0.13-7	0.98	25	710⁻⁴5	0.99	2,3,3',4'
414[e]								3,3',4,4'
51[d]								
52[d]								
53	B	1.4	0.13-7	0.91	16	7-15	1.00	2,2',3,5',6
54	A	1.4	0.13-3	0.64				2,2',3,5',6
55	A	2.1	0.13-7	0.99				2,2',3,5,5'
56	B	2.6	0.13-7	0.95	35	7-90	0.95	2,2',4,5,5'

TABLE III-4 (cont.)

Peak No.	Type	Type A and Type B (I)			Type B (II) and Type C			Structure
		t_1 (day)	Duration[c] (day)	r	t_2 (day)	Duration[c] (day)	r	
88	C				>90	0.13-90		2,2',3,3',4,4',5,5'
89[e]								
91[f]								2,2',3,3',4,5,5',6,6'
92[f]								2,2',3,3',4,4',5,6,6'
93[f]								2,2',3,3',4,4',5,5',6

[a]Source: Tanabe et al., 1981

[b]Oral administration of a mixture of Kanechlors 300, 400, 500 and 600 (1:1:1:1)

[c]Period for the calculation of biological half-lives.

[d]Not detected because of the disappearance of PCB peaks <0.13 days after administration.

[e]Not determined.

[f]Degradated in alkaline digestion process.

t_1 = Biological half-lives of Type A PCBs and of initial regression of Type B PCBs.

t_2 = Biological half-lives of Type C PCBs and of subsequent regression of Type B PCBs.

r = Correlation coefficients obtained from linear regressions.

Long-term kinetics of 2,2',4,4',5,5'-hexa-CB have been studied in rats maintained at a constant adipose tissue mass (Wyss et al., 1986). Table III-5 indicates that under these conditions, the majority of the body burden of this isomer is relegated to the fat compartment with the skin accumulating the next highest load. There is a striking persistence of this congener, with 49% of the dose still associated with tissue compartments 280 days after dosing. The half-times for specific compartments are given in Table III-6. Levels in tissues generally decline in a triphasic fashion with half-times of the terminal component on the order of 450 days. As seen in Table III-7, only minimal amounts of 2,2',4,4',5,5'-hexa-CB are excreted in urine. Extrapolation to infinite time points predicts that ~83% of the total dose will eventually be excreted in the feces with a half-time of 478 days. Owing to its persistence and extremely long half-time for elimination, this particular congener has a high potential for accumulation within the body.

The pharmacokinetics of PCB mixtures and congeners in several other species including the dog, fish, mink, avian species and swine have been reported (Sparling and Safe, 1980b; Lutz et al., 1984; Sipes et al., 1982a,b; Hansen et al., 1983; Brunn, 1984; Hornshaw et al., 1983; Gruger et al., 1975; Guiney et al., 1979; Guiney and Peterson, 1980). The results are somewhat comparable for all species with long-term accumulation of individual PCBs occurring primarily in adipose tissue. It was apparent that rates of PCB metabolism were important with respect to tissue persistence of individual compounds. Sparling and Safe (1980b) suggested that the degree of ortho-chloro substitution (Cl-2; Cl-6) may contribute to the ultimate

TABLE III-6

Tissue Kinetics of 2,2',4,4',5,5'-Hexa-CB in Rats with Constant Adipose Tissue Mass[a,b]

Tissue	Half-life for Removal		
	α-Phase	β-Phase	γ-Phase
Blood	0.114	8.4	462
Liver	0.161	9.9	442
Lung	0.182	12.3	433
Muscle		12.1	478
Brain		17.3	449
Skin		13.9	431
Adipose		10.9	456

[a]Source: Adapted from Wyss et al., 1986

[b]Half-lives are given in days.

persistence of PCBs in various species. A mixture of 2,2',4,4',6,6'-, 2,2',4,4',5',6'-, 2,2',4,4',5,5'-, 2',3,4,4',5,5'- and 3,3',4,4',5,5'-hexa-CBs (1:1:1:1) was administered by gastric gavage to rats, guinea pigs, rabbits, Japanese quail and trout, and the concentrations in the fat or whole carcass were determined after 29 days (Table III-8). These isomers are all relatively resistant to metabolism but contain 0-4 ortho chlorine substituents (Cl-2; Cl-6). The total hexa-CB levels in rat, rabbit and guinea pig fatty tissue were 8.27, 6.84 and 4.74 ppm, respectively: whereas 3.02 and 2.15 ppm of the hexa-CBs were detected in the trout and Japanese quail carcasses, respectively. The extent of ortho-chloro substitution markedly affected the levels of the individual hexa-CB isomers retained in the test animals. In the rat, the di-ortho substituted analog was preferentially retained over the other isomers whereas the coplanar most toxic isomer, 3,3',4,4',5,5'-hexa-CB, was present in the lowest concentration. The rabbit and guinea pig preferentially retained the hexa-CBs with 0, 1 and 2 ortho-chloro substituents, the Japanese quail retained only the 3,3',4,4',5,5'-hexa-CB isomer, whereas no striking preferences in hexa-CB isomer retention was observed in the trout. The marked differences in the retention of hexa-CB isomers with 0, 1,2,3 and 4 ortho-chloro substitution by different animal species should be considered in chronic toxicity studies, since the most toxic polychlorinated biphenyls have minimal (1 or 0) ortho-chloro substituents.

The critical or rate limiting event in the elimination of PCBs is metabolism. The major site of metabolism is the hepatic cytochrome P-450 dependent monooxygenase system. Species variation in the intrinsic metabolism of PCBs demonstrates that different species have different basal capacity to metabolize these compounds. This difference in metabolic capacity is reflected ultimately in the elimination half-lives of the PCBs.

Table III-9 summarizes data on the in vitro hepatic metabolism and in vivo metabolic clearance of 2,2',3,3',6,6'-hexa-CB, 4,4'-di-CB, and 2,2',4,4',5,5'-hexa-CB in humans, monkeys, dogs and rats (Schnellmann et al., 1985). Significant species variation was found in the microsomal metabolism of PCBs. For each PCB, the V_{max} values for metabolism in the monkey, dog and rat are consistent with the respective metabolic clearance values generated from in vivo studies. For example, the monkey metabolized 2,2',3,3',6,6'-hexa-CB at a faster rate than 4,4'-di-CB and did not metabolize 2,2',4,4',5,5'-hexa-CB. The in vivo metabolic clearance values indicate that 2,2',3,3',6,6'-hexa-CB was eliminated faster than 4,4'-di-CB, which in turn was eliminated faster than 2,2',4,4',5,5'-hexa-CB. The metabolic clearance of 2,2',4,4',5,5'-hexa-CB in the monkey is <1 mℓ/min and only 18% of a dose of this isomer is excreted over 90 days (Sipes et al., 1982a; Lutz et al., 1984). In general, the findings with the rat were similar to those observed in the monkey. Unlike the rat and monkey, the dog metabolized 2,2',4,4',5,5'-hexa-CB in vitro. This result is consistent with the fact that the dog eliminated 50% of a dose of 2,2',4,4',5,5'-hexa-CB in 8 days, while the monkey and rat were incapable of eliminating 50% of the administered dose during their remaining lifespan (Lutz et al., 1977; Kato et al., 1980; Sipes et al., 1982a). In summary, the kinetic constants for PCB metabolism obtained from the dog, monkey and rat hepatic microsomal preparations were good predictors of in vivo metabolism and clearance for the three PCBs.

Pharmacokinetic Studies in Humans

In investigations directed at determining which species most accurately predicts the metabolism and disposition of PCBs in humans, the in vitro metabolism of 2,2',3,3',6,6'-hexa-CB, 4,4'-di-CB, and 2,2',4,4',5,5'-hexa-CB was also investigated in human liver microsomes (Schnellmann et al., 1983, 1984). Data in Table III-9 suggest that the human metabolism of PCBs would most closely resemble that of the rat and monkey, but not the dog. There is good agreement between the V_{max} values generated from the human and rat preparations, whether expressed per nmole P-450 or per mg microsomal protein (Schnellmann et al., 1985). Since hepatic cytochrome P-450 concentration are relatively similar in the human and the rat, Schnellmann et al. (1985) concluded that the rat would be a good model for human PCB disposition studies.

In vivo data on the relative persistence of specific PCBs in humans are also consistent with the above in vitro results on the metabolism of PCBs. Jensen and Sundstrom (1974) reported that 2,2',4,4',5,5'-hexa-CB was the PCB congener found in the highest concentration in human adipose tissue, while 2,2',3,3',6,6'-hexa-CB was not detected. Since both compounds are found in commercial PCB mixtures and in the environment, the presence of 2,2',4,4',5,5'-hexa-CB in adipose tissue is apparently related to the resistance of this congener to biotransformation and elimination (Sissons and Welti, 1971; Albro et al., 1981). Other investigators have measured the comparative rates of elimination of individual PCBs from the blood of PCB-poisoned patients in Taiwan (Chen et al., 1982). They found that the blood concentration of 2,2',4,4',5,5'-hexa-CB only decreased 10% over 300-500 days. This suggests that this PCB is not readily eliminated and, is, commercial PCB product). For example the PCB composition of serum or adipose tissue of workers exposed to the lower chlorinated PCB product, Aroclor 1016, is significantly different than observed in Yusho patients and there is bioconcentration of the more persistent lower chlorinated congeners such as 2,4,4'-tri-CB, 2,4,4',5-tetra-CB, 2',3,4,4'-tetra-CB and 2,3',4,4',5-penta-CB (Wolff et al., 1982b), which are present in the commercial product. The more familiar higher chlorinated PCB congeners that bioconcentrate from environmental sources are also evident (at relatively lower concentrations) in the gas chromatograms of occupationally-exposed worker's tissue extracts.

Chen et al. (1982) investigated the elimination of individual PCBs from the blood of PCB-poisoned humans in Taiwan. The results indicate that tetra- and pentachlorobiphenyls with adjacent unsubstituted carbon atoms at meta-para positions are rapidly eliminated from the blood of patients, while PCBs with the same degree of chlorination but with adjacent unsubstituted carbon atoms at ortho-meta positions are eliminated more slowly. They calculated terminal half-lives of 2,4,5,3',4'-penta-CB and 2,3,4,3',4'-penta-CB in the blood of exposed humans to be 9.8 ± 5.0 and 6.7 ± 2.5 months (means $\pm$ SD), respectively.

Fetal and Neonatal Studies

Several studies (Torok and Weber, 1981; Masuda et al., 1978, 1979; Orberg, 1977; Curley et al., 1973; Baker et al., 1977; Mizunoya et al., 1974; McCormack et al., 1979; Allen and Barsotti, 1976; Iatropoulos et al., 1978; Bailey et al., 1980; Takagi et al., 1976; Ando, 1978; Vodicinik and Lech, 1980; Vodicinik, 1986) clearly demonstrate that PCB mixtures and

TABLE III-10 (cont.)

Species/Strain	Sex/Number	Source of PCBs	Vehicle	Dosage/ Route of Administration	Distribution to Dams Milk or Offspring	Reference
Rat/Sprague-Dawley	F/NR	Aroclor 1254	diet	0, 25 or 50 mg/kg diet starting day 8 of gestation - day 14 postpartum	Dam: fat>mammary>kidney>liver>lung Milk: postpartum day 0/293 mg/mℓ/50 mg/kg; postpartum day 14/32 μg/mℓ/50 mg/kg	McCormack et al., 1979
Monkey/rhesus	F/16	Aroclor 1248	diet	0, 2.5 or 5.0 mg/kg diet continuously 1.5 years, start 6 months prebreeding	Stillborn male-5.0 mg/kg: lung>pancreas> adrenal>thymus>spleen>muscle>kidney> liver. Male died at 44 days-2.5 mg/kg: bone marrow~lung>thymus>adrenal>pancreas> kidney>spleen.	Allen and Barsotti, 1976
Monkey/rhesus	F/3	Clophen A-30	1% methyl cellulose in water	0 or 16 mg/kg bw/day by gavage 22-29 days	Blood of offspring higher in PCBs than blood of dams. PCB levels in milk 10-20 times that of serum of dam. Higher PCB levels in tissues of infant than dam.	Iatropoulos et al., 1978; Bailey et al., 1980
Rat/JCL-CD	F	Radiolabeled Kanechlor 400	Olive oil	oral administration once a week from day 8-18 of pregnancy	70-56% of dose excreted by dams (skin and placenta-major fetal deposition). Average dam-fetal transfer 28% of dose. Average amount of PCBs transferred by lactation (45 days) - 2% of dose. Nursing rat levels of PCBs lower than dosed pregnant or nonpregnant rats.	Takagi et al., 1976
Rats/Wistar	F	Radiolabeled 2,2',4,4',5,5'-hexa-CB	Olive oil	i.p. administration	Transfer by placenta and lactatum was 2.7 and 39.2%, respectively.	Ando, 1978
Mice/Sprague-Dawley	F	Radiolabeled 2,2',4,4',5,5'-hexa-CB	Corn oil	compound injected i.p. 2 weeks prior to mating	Transplacental transfer of PCB was minimal; after 20 days postpartum, lactation transferred most of the mothers dose to suckling pups.	Vodicinik and Lech, 1980
Mice/ICR	F	Radiolabeled 2,2',4,4'-tetra-CB	Corn oil	i.p. injection of 150 mg/kg on day 15 of gestation	Transplacental transfer ~1% of maternal body burden, 90% of maternal body burden eliminated over a 4-day nursing period.	Vodicinik, 1986

TABLE III-11

Transfer of [^{14}C]Hexa-CB from Mother Mice to Nursing Offspring[a]

Day of Sacrifice	Mothers[b]			Offspring[c]		
	mg Hexa-CB/ Total Carcass	µg Hexa-CB/g Litter	Percentage Total Dose Eliminated[d]	mg Hexa-CB/ Litter	µg Hexa-CB/ Litter	Percentage of Mother's Dose Accumulated
Day 19 pregnancy	0.862	5.12	0		-	-
Birth	-	-	2.7		-	-
Day 5 postpartum	0.372	8.59	56.8	0.545	15.31	3.00[e]
Day 10 postpartum	0.167	3.48	80.6	0.810	13.97	94.0
Day 15 postpartum	0.038	0.87	95.6	0.743	11.18	86.2
Day 20 postpartum	0.016	0.37	98.1	0.900	12.50	104.4

[a]Source: Vodicnik and Lech (1980)

[b]Virgin female mice pretreated with 50 mg/kg [^{14}C]2,2',4,4',5,5'-hexa-CB (~1.25 mg/animal) 2 weeks before mating. Each value represents the mean of two carcasses.

[c]Each value represents the mean from the carcasses of two pooled litters.

[d]Represents percentage eliminated from dose remaining in mothers at day 19 of pregnancy.

Bailey et al., 1980). The youngest infant and her dam became moribund on exposure day 21. Necropsy of the infant revealed mild hepatocellular pathology and dilation of renal tubules containing casts. Levels of PCBs in milk appeared to range from 10-20 times the levels in serum. In general, serum levels of PCBs in infants were about 2 times the levels in their dams. Body fat contained the highest levels (1687 μg/g) > bone marrow > lymph nodes > adrenals > thymus > kidney > spinal cord > liver (80 μg/g). In all tissues except the thymus, infant tissue levels were 1.94-5.47 times the corresponding levels in the moribund dam sacrificed after 22 days of exposure. These studies confirm the importance of lactation as the major source of PCB exposure in neonates.

The importance of lactation as a major route for PCB excretion was demonstrated in a study of a woman occupationally exposed to Kanechlor 300 and 500 in a capacitor factory (Yakushiji et al., 1978). The PCB levels in the tissues and fluids from the mother and child are summarized in Table III-12. Since PCB levels in umbilical tissues, umbilical blood and amniotic fluid were considerably less than measured in mothers blood it was evident that there were some barriers to transplacental exposure to these toxins. Other recent studies confirm this observation (Jacobson et al., 1984; Bush et al., 1984). Since the mother's milk and serum contained unusually high levels of PCBs, the baby was not nursed on her breast milk. Lactation of this individual resulted in the excretion of 200 mg of PCBs in 818 ℓ of breast milk and resulted in an overall 76% decrease in (milk) PCB levels.

These data clearly illustrate the importance of lactation as the major route of infant PCB exposure and as a major route of depuration for the highly exposed mothers.

Metabolism

As discussed previously in this chapter, the major factor that affects the long-term persistence of individual PCBs in animal tissues is the rate of metabolism of these compounds. It was initially shown by Block and Cornish (1959) that the lowest chlorinated biphenyl, 4-CB, was metabolized to give 4'-chloro-4-biphenylol and its glucuronide as urinary metabolites. Hutzinger et al. (1972) reported that not only 4-CB but several higher chlorinated biphenyls were metabolized to give hydroxylated and dihydroxylated PCB products as determined by MS analysis. These initial results also suggested the rates of metabolite excretion were species-dependent (for example, rats > birds > fish) and dependent on the degree of substrate chlorination since only trace levels of the higher halogenated biphenyl metabolites were detected.

The *in vivo* metabolism of individual PCBs by mammalian, avian and plant species and by microorganisms has been reviewed (Matthews and Dedrick, 1984; Schnellmann et al., 1985; Safe, 1980; Sundstrom et al., 1976a). Numerous studies have focused on delineating the problems associated with PCB metabolism, and these include structure determination of PCB metabolites, evaluation of the effects of the position and number of chloro substituents on the sites, and rates of metabolism and determination of the mechanism of PCB metabolism (that is, metabolic pathways).

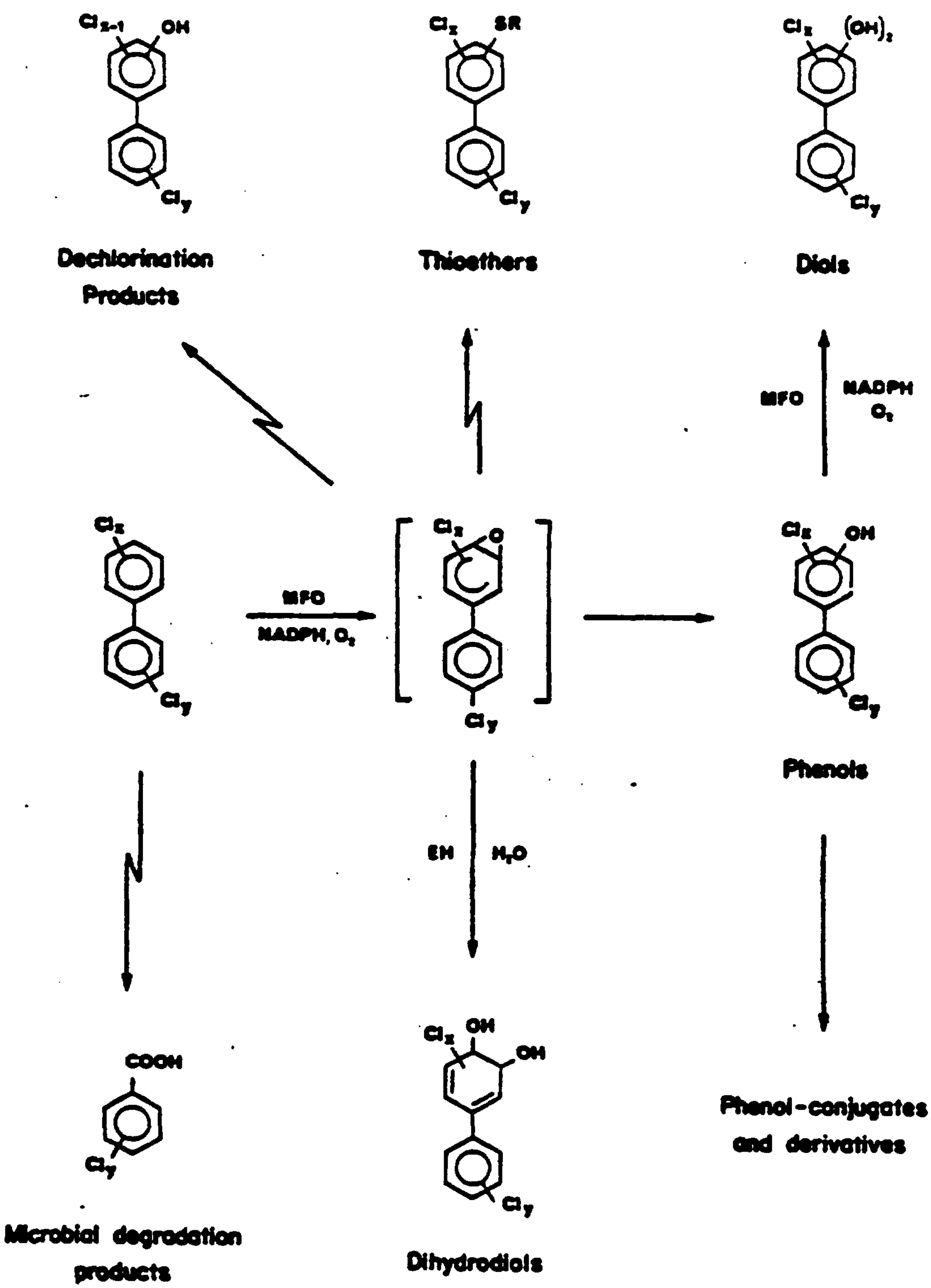


FIGURE III-2

Summary of PCB Metabolism

Source: Safe, 1980

^2H) and the results were consistent with metabolism by arene oxide intermediates. Thus, the detailed metabolic studies of selected PCB isomers and congeners suggested that arene oxides play a major role in their metabolism.

Metabolically mediated cytotoxicity, mutagenicity and carcinogenicity have been associated with the in vivo formation of electrophilic species and their subsequent alkylation of critical cellular macromolecules. Arene oxides are potential electrophiles and thus their formation and subsequent cellular reactions can involve the formation of both detoxification products (for example, metabolites, glutathione conjugates, other phase II conjugates), which are excreted, and potentially toxic covalently bound substrate-macromolecular adducts. The in vivo and in vitro formation of PCB-protein, RNA and DNA adducts have been reported in several studies (Wyndham and Safe, 1978; Wyndham et al., 1976; Hesse and Wolff, 1977; Hesse et al., 1978; Shimada and Sato, 1978; Stadnicki et al., 1979; Wong et al., 1979; Morales and Matthews, 1979). The in vivo binding of 2,2',4,4',5,5'- and 2,2',3,3',6,6'-hexa-CB to hepatic protein, RNA and DNA in mice has been reported (Morales and Matthews, 1979). Moreover, the in vitro metabolism of numerous PCB isomers and congeners by rabbit, rat, mouse and monkey liver microsomal enzymes results in the formation of hydroxylated metabolites and covalently bound PCB-macromolecular adducts (Wyndham and Safe, 1978; Wyndham et al., 1976; Hesse and Wolff, 1977; Hesse et al., 1978; Shimada and Sato, 1978).

In vitro studies using mammalian cells in culture have confirmed DNA damage mediated by PCB congeners and their metabolites. Incubation of 2,2',5,5'-tetra-CB, 2,2',5,5'-tetrachloro-4(3)-biphenylols (4:1 mixture of tissue and skin reflects the high affinity of the PCBs for lipophilic tissues. At equilibrium the elimination of PCBs from all tissues will be dependent on the structure-dependent metabolism rates of individual PCB congeners. For example, biological half-lives in the rat range from 0.15 days for 2,2'-di-CB to ~460 days for 2,2',4,4',5,5'-hexa-CB.

Metabolism is apparently the primary rate limiting event regulating the elimination of PCBs from mammalian systems. The *in vitro* metabolism of PCBs has been investigated in liver microsomes from the human, monkey, dog, and rat. The data suggest that the human metabolism of PCBs would most closely resemble that of the rat. Therefore, the rat should be a good model for predicting the disposition of PCBs in humans.

The position and degree of chlorination substantially influence the rate and extent of PCB metabolism. As the degree of chlorination increases on both phenyl rings the rate of metabolism decreases, though there is also a selectivity with respect to type of substitution for isomers. The availability of two vicinal unsubstituted carbon atoms facilitates metabolism of the PCB substrate but is not a necessary requirement for metabolism. Although phenolic products are the major PCB metabolites, sulfur-containing metabolites, trans-dihydrodiols, polyhydroxylated PCBs and their methyl ether derivatives have been identified. The presence of trans-dihydrodiol metabolites strongly suggests metabolism through an arene oxide intermediate. Arene oxides have been implicated in cellular necrosis, mutagenicity and carcinogenicity; however, the role of metabolism in the genotoxicity of PCBs has not been delineated.

IV. HUMAN EXPOSURE

Humans may be exposed to PCBs from a variety of sources including food, ambient air, occupational settings and consumer products. This section is limited to water, food and ambient air because these media are considered to be sources common to all individuals. Evidence of human exposure to PCBs from finished drinking water is limited. The bulk of the information relates to the years 1984-1986.

Water

United States. The National Organic Monitoring Survey (NOMS) was conducted in 1976 to determine the frequency of occurrence of specific organic chemicals (including PCBs) in finished water supplies of 113 cities nationwide (U.S. EPA, 1977). Data from three phases (referred to as NOMS I, NOMS II and NOMS III) of the study were collected over an 11-month period (March 1976 to January 1977) to reflect any long-term or seasonal variations.

PCBs were not found in groundwater supplies sampled in NOMS I (minimum quantifiable limit = 0.12 μg/ℓ). Only a single finished groundwater sample in each of NOMS II and NOMS III contained detectable levels of PCBs (~6% frequency of occurrence for both phases). Concentrations of 0.1 μg/ℓ were reported for the NOMS II and NOMS III samples (minimum quantifiable limits ranged from 0.1-0.2 μg/ℓ, respectively).

During a groundwater study in the state of New Jersey, Tucker and Burke (1978) examined 163 wells in all nine counties of the state, including public and private drinking water wells, and wells near industrial sites and

The Aroclor 1016 origin was confirmed by identifying at least five specific surrogate congeners by retention time from a possible 19 congeners. The 19 congeners were: 4-Cl-CB/2,2'-Cl_2-CB (also Aroclor 1221); 2,4'-Cl_2-CB (also Aroclor 1221); 2,2',5'-Cl_3-CB; 2,2',4'-Cl_3-CB; 2,2',3'- and 3,2',6'-Cl_3-CB; 4,2',6'-Cl_3-CB; two unidentified Cl_3-CBs; 3,3',5'-Cl_3-CB; 3,2',4'-Cl_3-CB; 2,4,4'-Cl_3-CB (also Aroclor 1221); 2,3',4'-Cl_3-CB; 2,5,2',5'-Cl_4-CB (also Aroclor 1254); 2,4,2',5'-Cl_4-CB (also Aroclor 1254); 2,3,2',5'-Cl_4-CB (also Aroclor 1254); 2,4,2',4'-Cl_4-CB (also Aroclor 1254); 2,3,2',3'-Cl_4-CB (also Aroclor 1254); and two unspecified Cl_4-CBs (one of which also arose from Aroclor 1254). Thus, 10 of the 19 congeners were unambiguously from Aroclor 1016, with 6 being resolved specific congeners. In this study, 60 congeners were utilized to identify the possible presence of Aroclors 1221, 1016, 1254 and 1260. Each peak chosen provided an independent estimate of the quantity of the Aroclor using the appropriate response factor for each congener. The concentration of the Aroclor was calculated as the average of the concentrations by each of the five chosen peaks. Representative samples were confirmed by GC/MS. The detection limit was 50 pg, equivalent to a 12 ng/ℓ (12 ppt) concentration in 2 ℓ of water subjected to the analysis technique.

In raw tap water in the Waterford, NY treatment plant, which also has the Hudson River as its source, mean PCB levels in 1976 were 0.12 μg/ℓ (range: 0.05-0.24) (Schroeder and Barnes, 1983). The average efficiency of PCB removal was 80-90% at high and low flows with levels in the treated drinking water seldom exceeding 100 ng/ℓ.

September each year declined from 0.68 μg/ℓ in 1977 to 0.11 μg/ℓ in 1982. PCB transport declined below river flows of 400 m^3/second. During low flow conditions, most of the PCB penetrates a 0.45 μm filter whereas this is not so at high flow. Also, the less chlorinated congeners are present in greater proportions in the filtrate than in the nonfilterable residue. At high flow, the more chlorinated congeners dominate in whole-water samples. In the late 1970s, waters from the tidal Hudson contained generally 0.1-0.2 μg/ℓ as dissolved PCBs; in 1982, the range was reported as 0.05-0.10 μg/ℓ. Particle size and organic content appear to control PCB content in the Hudson River.

Bush et al. (1985a) identified the PCB congeners in Hudson River water sampled on July 6 and August 15, 1983 at Roger's Island, Thompson's Island and Stillwater (Table IV-1). The respective total PCB concentrations in July were 100, 532 and 266 μg/ℓ, respectively; in August, the concentrations were 331, 586 and 243 ng/ℓ, respectively, mostly as Aroclor 1221, 1242, 1254 and 1260. A specific congener analysis is presented in Table IV-1 for the three sites. The levels primarily reflected dissolved PCBs since very little sediment was present in all samples. A surprising feature of the results was that half of the transport appeared to be caused by only three low chlorinated PCB congeners (2-, 2,2'- and 2,6-PCB). The levels of more chlorinated Aroclors did not vary greatly from site to site, but those of Aroclors 1221 and 1242 did.

Baker et al. (1985) reported that resuspension events in midsummer in Western Lake Superior waters resulted in a 50% increase in PCB residues in the period May to October, 1983. The seasonal cycling of PCB congeners at 12 sampling sites was strongly dependent on their degree of chlorination

TABLE IV-1 (cont.)

Congener	Aroclor	July			August		
		RI	TI	ST	RI	TI	ST
2,4,2',4',5'	54/60	1.2	2.9[b]	5.7[b]	14	45	6
2,3,2',4',5'	54/60	1.0	1.0	1.9	1.6	1.6	0.6
2,5,2',3',4	54/60	0.4	0.9	1.1	8.0	2.9	1.8
2,4,2',3',4'	1254	1.6	1.5	1.6	2.6	4.4	1.3
2,3,2',3',4'	54/60	2.4	2.5	2.6	0.7[d]	5.5	2.0
2,5,2',3',5',6'	54/60	0.6	0.5	1.9	0.3	0.7	0.4
2,3,2',3',5',6'	54/60	ND	ND	0.2	3.3	6.7	0.0
2,3,4,2',3',6'	54/60	0.2	0.7	0.9	1.3	2.5	0.9
3,4,3',4'	1254	0.8	0.7	0.7	3.5	28	2.0
2,3,6,2',3',4',6'	54/60	0.5	0.6	0.7	1.8	2.3	2.3
2,4,5,2',4',5'	54/60	ND	ND	ND	0.9	1.2	0.3
2,3,4,2',4',5'	54/60	2.8	1.9	0.4	2.3	2.2	1.0
3,4,2'3',4',6'	54/60	1.6	1.6	0.5	2.8	1.7	0.3
2,3,4,2',3',4'	54/60	1.7	1.4	1.0	1.0	0.8	0.04
2,3,6,2',3',4',5',6	54/60	ND	ND	ND	120	85	50
3,4,2',3',4',5'	54/60	9.4	9.4	11	0.2	0.2	ND
2,3,4,5,2',3',5',6'	1260	0.03	0.5	0.3	0.2	0.4	0.1
Total PCB		100	532	266	331	586	243

[a]Source: Bush et al., 1985a

[b]Probability that sites identical <0.005

ND <0.01 ng/ℓ

Superior sediments taken in 1982, a similar analysis showed an Aroclor 1242 composition which varied between 15 and 21% (the rest being Aroclor 1254) at Aroclor 1242 levels between 1.5 and 1.9 ng/g sediment.

In a laboratory experiment (Vitkus et al., 1985), 208 mg of applied Aroclor 1254 in wastewater influent was diluted to a biochemical oxygen demand (BOD) of 200 ppm so that the Aroclor 1254 concentration was 1 ppm. After treatment with a lab-scale, fixed biomass for up to 17 weeks, 54% of the PCB was recovered in effluent plus biomass. At 1 ppb levels, all of the Aroclor was recovered in the effluent plus biomass. Volatilization (30-39% of that applied) also accounted for substantial loss of the Aroclor at the 1 ppm level. The chemical oxygen demand (COD) and BOD removal even at 1 ppm Aroclor 1254 remained between 80 and 100% after week 3. There was no toxicity to the biomass even at exposure levels of up to 100 ppm for 2 days. The U.S. EPA has estimated that industrial and publically-owned waste treatment facility effluents are responsible for an annual discharge of 110.08×10^3 kg of PCBs into U.S. waters, and this has resulted in PCB levels of 100-3000 ng/ℓ in waters and 2.0-160 μg/kg in sediment. The sedimentation process in wastewater treatment plants primarily removes settleable particles that contain high levels of adsorbed PCBs (Garcia-Gutierrez et al., 1982; McIntyre et al., 1981).

PCBs (Aroclor 1260) have been detected in rainfall, street particulates, run-off and basin soils (4/11 samples) of the Fresno Metropolitan Flood Control District, California, which relies on aquifer recharge basins for stormwater retention (Salo et al., 1986).

Table IV-2. PCBs in Rain and Snow Around the World

PCB	Concentration	Sample Type	Sample	Collection Period	Location
Total	0.1 g/m^2 -day-10^7	Bulk deposit; unfiltered	Bulk collector - glass sheet coated with mineral oil	Event basis; 2/71	Suburban La Jolla, CA, USA
	n.d. 130 ppt	Bulk deposit; unfiltered	Unknown	Variable weekly monthly periods: 7/74-11/74	Chesapeake MD, USA
	50-230 ppt[b]	Snow; unfiltered	Unknown	Event basis; 1974-1976	Remote, urban Lake Superior, USA
	97.5-229 ppt	Snow; unfiltered	Unknown	Event basis; 1974-1976	Remote, urban Lake Michigan USA
	21 ng/l[b]	Rain; unfiltered	Bulk collector - stainless steel w/glass reservoir	Event basis; 5/76 - 11/76	Rural Great Lakes, Canada
	29 ng/l[b]	Snow; unfiltered	Bulk collector - aluminum sheet w/ manual packing into containers	Event basis; winter 1975-76	Rural Great Lakes, Canada
	21-28 ng/l[b]	Rain; unfiltered	Bulk collector - stainless steel funnel w/glass reservoir	Event basis; 5/76-11/76 5/77-11/77	Rural Great Lakes, Canada
	29 ng/l[b]	Snow; unfiltered	Manual collection bulk sample	Accumulated snowpack; fall thru winter, 1975-76	Rural Great Lakes, Canada
	14-138 ng/l[b]	Rain, snow; aqueous, particulate; wet only	(1) Bulk collector - galvanized steel funnel with particulate filter and adsorbant cartridge ; *in situ* extraction & (2) Auto. wet-only collector (HASL)	Event basis; 1975-1978	Rural, urban Lakes Huron & Superior, USA
	9-158 g/km^2 yr[b]	Bulk deposit; unfiltered	Bulk collector - metal cylinder	Monthly samples 1975-1978	Rural, urban Lakes Huron & Superior, USA

Table IV-2 (cont.)

PCB	Concentration	Sample Type	Sample	Collection Period	Location
Total	Unknown	Rain; unfiltered	Unknown	Event basis	Urban Lake Zurich, Switzerland
	178-6010 ng/ m^2-100 days	Rain; aqueous	Bulk collector - aluminum funnel w/ adsorbent cartridge; in situ extraction	3-mo. period: 6/75 - 5/76	East coast United Kingdom: network
Aroclor 1016	1300 ng/l	Bulk deposit; unfiltered	Automatic Wong Sampler	Weekly collection or 30-day composite sample	Urban Fort Edward, NY USA
Aroclor 1242	39-57 ng/ l[b,c]	Rain; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in situ extraction	Event basis; 7/75-1/77	Rural, urban Lake Michigan USA
	16-31/ng/ l[b,c]	Rain; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbant cartridge; in situ extraction	Event basis; 7/75-1/77	Rural, urban Lake Michigan USA
	41 ng/ l/[bc]	Snow; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbant cartridge; in situ extraction	Event basis; 7/75-1/77	Rural, urban Lake Michigan USA
	33 ng/ l[b,c]	Snow; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbant cartridge; in situ extraction	Event basis; 7/75-1/77	Rural, urban Lake Michigan USA
	<0.6 ng/l[b]	Rain; unfiltered	Bulk collector - Stainless steel funnel with glass reservoir	Event basis; 4/79-8/79	Remote Enewetak Atoll, Pac. Ocean
Aroclor 1254	<3-24 ng/kg rain	Rain; unfiltered	Bulk collector - stainless steel bowl	Event basis spring/fall 1977-1979	Coastal SC, USA

Table IV-2 (cont.)

PCB	Concentration	Sample Type	Sample	Collection Period	Location
Aroclor 1260	11 ng/l[b,c]	Snow; aqueous	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in-situ extraction	Event basis 7/75-1/77	Rural, urban Lake Michigan
	24 ng/l[b,c]	Snow; particulate	Bulk collector - galvanized steel funnel w/particulate filter & adsorbent cartridge; in-situ extraction	Event basis; 7/75- 1/77	Rural, urban Lake Michigan USA
Polychlorinated terphenyl (PCT)	Unknown	Rain	Unknown	Unknown	Unknown

[a]Source: Mazurek and Simoneit, 1985
[b]Mean concentration

for fiscal year 1979 (FDA, 1982a,b). The relative daily intakes of PCBs are presented for FY74 through FY79 in Table IV-3. There is no apparent trend in intake levels over the years for which information was obtained. Total dietary intake of PCBs for adults in FY79 was 0.0133 μg/kg/day (FDA, 1982a). [This includes an estimated 0.0053 μg/kg/day from dairy products, 0.0075 μg/kg/day from meat, fish and poultry, and 0.0005 μg/kg/day from oils and fats.]

No PCBs were detected for infant and toddler dietary studies by FDA in FY79 (FDA, 1982b). Total dietary intakes of PCBs for infants and toddlers in FY78 (as reported in FDA, 1982b) were 11.3 and 98.5 ng/kg/day, respectively. Information on the individual food groups, which included the total intake values, was not obtained. The FDA calculations assume that the average infant weighs 8.2 kg (6-month-old) and the average toddler (2-year-old) weighs 13.7 kg. No comparisons of intakes of PCBs by geographic region were presented in the FDA Market Basket Studies.

Bioaccumulation of PCBs in fish and other aquatic life is a major route of exposure to humans.

<u>PCB Residues in Aquatic Life of the United States and Canada</u>. The PCB pollution in the Hudson River in the United States has been discussed (Brown et al., 1985). The monitoring of PCB levels in fish in 1977 showed that a PCB contamination problem existed (the levels were well above the then FDA temporary tolerance level of 5.0 ppm). Since 1977, not only fish but net-spinning caddis fly larvae (*Trichoptera*:*Hydropsychidae*) have been monitored from June through September. Zooplankton (e.g., *Gammarus*, *Neomysis*, *Leptodera* and *Crangon*) have also been monitored. Levels are higher in the

upper river than those in the lower river and have been steadily declining ever since remedial actions have been completed in 1977. Mean total PCB concentrations in fillets from largemouth bass (Micropterus salmoides) collected near Stillwater declined from 145.3 μg/g in 1977 to 10.2 μg/g in 1981; at Catskill in the estuary, the residues decreased from 29.5 μg/g in 1977 to <1.0 μg/g in 1981. PCB concentrations in median striped bass (Morone saxatilis) declined from 9.9 μg/g in 1978 to 2.6 μg/g in 1982. During the same period, the fish showing levels below the FDA temporary tolerance level increased from 11-75%. In 1983, only 10% of the fish were below the current FDA limit of 2.0 ppm.

A strong correlation between PCB and lipid concentrations was observed for all Hudson River resident species but not for anadromous (river-spawning) species. For example, mean lipid-based PCB concentrations in yearling pumpkinseed (Lepomis gibbosus) declined from 1079 μg/g in 1979 to 36 μg/g in 1982. Similarly, mean lipid based PCB concentrations in brown bullhead (Ictalurus nebulosus), goldfish (Carassius auratus), and largemouth bass (Micropterus salmoides) declined from 2.51, 6.76 and 6.01 mg/g to 0.428, 0.310 and 1.000 mg/g, respectively. Between 1978 and 1981, a progressive decline in PCB levels also generally occurred in zooplankton, especially in Gammarus spp. In samples of resident and anadromous fish, the pattern of decline in total PCB concentration is dominated by the decrease in Aroclor 1016. For example, in Gammarus spp, the mean was 1.5 ppm in 1979 and 0.76 ppm in 1980. During 1977-1982 in the summer, the water PCB concentrations correlated well with the PCB concentrations in yearling pumpkinseed collected in the fall at Stillwater. Though less correlated, the PCB levels in other fish species and in macroinvertebrates are still correlated in the upper Hudson River.

TABLE IV-4

Chlorinated Biphenyl Congener Concentration (μg/g net weight)

in Caddisfly Larvae taken from the Hudson River[a]

	Roger's Island				Thompson's Island						Stillwater	
	H. leo.		Chemo(g)		H. leo.		P. gut.		Chemo(g)		P. gut.	
Congener	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
2	.08	.05	.07	.04	.6	.2	0.3	0.1	.3	.04	.004	.002
2,2'	.03	.01	.05	.01	3.	.8	.2	.09	.8	.04	.1	.01
2,3'	.03	.01	.06	.01	.06	.02	.01	.008	.07	.002	.07	.002
2,4'	.04	.008	.06	.01	.5	.2	.05	.02	.3	.01	.01	.002
2,2',5'	.02	.01	.5	.1	1.2	.2	.1	.05	.6	.03	.08	.004
2,2',4'	.06	.03	.1	.03	.7	.1	.05	.02	.3	.07	.03	.001
2,2',3'+3,2',6'	.04	.02	.1	.03	0.	0.	0.	0.	0.	0.	0.	0.
4,2',6'	.1	.06	.4	.1	2.0	.4	.1	.04	.9	.02	.08	.004
4,4'	.06	.03	.09	.03	.3	.07	.2	.02	.1	.05	.3	.009
2,2',4',6'	.1	.04	.1	.06	1.1	.2	.06	.02	.4	.03	.03	.004
3,2',5'	.06	.02	.1	.02	1.0	1.0	0.	0.	0.	0.	.05	.05
3,2',4'	.1	.1	0.	0.	1.6	.07	.4	6.0	.8	.03	.7	.2
3,2',3'+4,2',4'	.2	.1	.8	.1	.7	.03	.09	.05	.8	.1	.06	.03
4,2',3'	.4	.2	.7	.2	2.6	.4	.2	.08	1.3	.05	.1	.03
2,5,2',5'	1.2	.5	2.3	.5	7.4	.9	.7	.1	3.1	.1	.5	.04
2,4,2',5'	.5	.2	1.0	.2	1.8	.2	.2	.04	.8	.06	.1	.01
2,3,2',5'	1.1	.5	2.3	5	12.	1.6	1.7	.07	3.5	.1	1.2	.2
2,4,2',4'	.3	.1	.7	.1	1.6	.2	.1	.02	.6	.03	.1	.01
CL4C	.5	.2	1.4	.3	2.5	.4	.1	.05	1.2	.03	.08	.01
CL4D	.6	.2	1.8	.4	3.7	.6	.3	.06	2.0	.06	.2	.06
2,3,2',3',6'	.07	.03	.2	.04	.5	.02	.05	.02	.4	.03	.02	.003
2,5,3',4'	.8	.3	1.6	.3	2.6	.1	.4	.03	1.2	.03	.2	.02
2,4,3',4'	.5	.2	1.1	.2	1.6	.2	.5	.05	.5	.01	.1	.02
2,5,2',4',5'	.2	.06	.3	.07	.9	.2	.1	.01	.6	.005	.07	.01
2,4,2',4',5'	.2	.06	.3	.06	.5	.2	.2	.02	.5	.006	.08	.04
2,3,2',4',5'	.1	.06	.3	.06	.6	.09	.1	.005	.4	.009	.07	.01
2,5,2',3',4'	.3	.1	.6	.1	1.3	.3	.1	.02	.5	.1	.08	.02
2,4,2',3',4'	.2	.8	.4	.9	1.4	.2	.2	.02	.7	.004	.2	.03
2,3,2',3',4'	.3	.1	.7	.1	1.8	.3	.2	.005	1.3	.02	.1	.01
2,5,2',3',5',6'	.01	.005	.02	.008	.3	.05	.02	.003	.2	.01	.01	.003
2,3,2',3',5',6'	.003	.003	.01	.004	.03	.004	0.	0.	.1	.1	.004	.002
2,3,4,2',3',6'	.05	.008	.1	.03	.4	.1	.06	.01	.4	.003	.04	.01
3,4,3',4'	0.	0.	.004	.002	.06	.06	0.	0.	.002	.002	.01	.006
2,3,6,2',3',4',6'	.2	.07	.4	.08	1.0	.01	.2	.03	.7	.1	.2	.02
2,4,5,2',4',5'	0.	0.	0.	0.	.3	.3	0.	0.	0.	0.	.3	.3
2,3,4,2',4',5'	.2	.05	.3	.06	.6	.2	.1	.02	.5	.05	.1	.006
3,4,2',3',4',6'	.03	.006	.04	.008	.1	.03	.03	.006	.2	0.1	.02	.002
2,3,4,2',3',4'	.03	.02	.02	.03	.2	.01	.04	.005	0.3	.04	.03	.008
3,4,2',3',4',5'	.02	.01	.05	.007	.1	.03	.004	.002	0.1	.001	.002	.002
2,3,4,5,2',3',5',6'	.02	.007	.02	.002	.09	.006	.01	.006	0.1	0.1	.008	.00002
Total	9.6	4.	22.	5.	66.	12.	8.	.7	31.	1.	6.0	3.

H. leo = Hydropsyche leonardi; Chemo(g) = Cheumatopsyche green phase; P. gut = pycnapsyche guttifier;

[a]Source: Bush et al., 1985a

in the flesh of the 12 year-old fish were ~13 ppm relative to wet weight, about the same levels as in aged trout taken from the same lake in 1970. The PCB resembled Aroclor 1254 but contained a higher proportion of more highly chlorinated isomers (higher Cl_6- and lower Cl_4-PCBs). The PCB accumulation in the flesh but not in the liver increased with fish age (3 fish/age): 6 years, 4.1-4.8 ppm; 7 years, 5.2-6.1 ppm; 8 years, 7.4-8.8 ppm; 9 years, 7.5-11.7 ppm; 10 years, 9.3-11.6 ppm; 12 years, 12.8-13.5 ppm (2 fish).

Fish are not the only edible animal known to accumulate PCBs from the Hudson River drainage area. PCBs have been measured in the subcutaneous fat and breast muscle of 55 waterfowl collected in New York State along the Hudson River and near Long Island during 1981 and 1982 (Kim et al., 1985). Waterfowl have relatively large amounts of fat, so it is possible that the FDA tolerance level for domestic poultry (3.0 μg/g) might be exceeded. Fifty-five waterfowl were examined for maximum PCB residues in terms of μg/g wet weight: 11 Canada geese (Branta canadensis) 0.63-15 (subcutaneous fat), 0.05-0.33 (breast muscle), and 0.08 (1 liver); 13 mallards (Anas platyrhynchos) 0.34-14 (subcutaneous fat), 0.07-1.1 (breast muscle), and 0.23 (1 liver); 18 black ducks (Anas rubripes) 0.59-20 (subcutaneous fat), 0.05-0.69 (breast muscle), and 0.16-0.29 (2 liver); 1 green-winged teal (Anas carolinensis) 0.81 (subcutaneous fat) and 0.27 (breast muscle); 1 hooded merganser (Lophodytes cacullatus) 124 (subcutaneous fat) and 6.3 (breast muscle); 1 shoveler (Anas clypeata) 8.8 (subcutaneous fat), 0.30 (breast muscle), and 0.21 (liver); 5 canvasback (Aythya valisineria) 0.98-13 (subcutaneous fat) and 0.11-0.66 (breast muscle); and 4 woodduck (Aix spousa) 0.64-9.0 (subcutaneous fat) and 0.08-0.12 (breast muscle). Levels in general were lower than in 1979 and 1980 samples. Sex and age were not

TABLE IV-6

PCB Residues in Freshwater Fish in the United States[a,b]

PCB Type	Sample Site/Years		Geometric Mean of PCB Concentration	
			Wet Weight (ppm)	Lipid Weight (ppm)
Aroclor 1248	107 U.S. stations (freshwater)	76/77	0.14	0.6
		78/79	0.14	0.8
		80/81	0.11	0.8
Aroclor 1254	107 U.S. stations (freshwater)	76/77	0.48	4.3
		78/79	0.46	5.0
		80/81	0.24	2.1
Aroclor 1260	107 U.S. stations (freshwater)	76/77	0.37	3.4
		78/79	0.37	3.6
		80/81	0.25	2.6
Total PCBs	107 U.S. stations (freshwater)	76/77	0.88	8.3
		78/79	0.85	9.6
		80/81	0.53	5.4

[a]Source: Schmitt et al., 1985

[b]Between 1976 and 1981, 935 samples were taken representing 62 taxa; in 1980 and 1981, 315 samples were taken representing 48 taxa.

Schmitt, 1986), from the Atchafalaya River basin in Louisiana in 1981 (Winger and Andreasen, 1985) and from Lake Verret, Plaquemire-Brule and East Franklin in Louisiana in 1978 and 1979 (Dowd et al., 1985).

Few PCB levels in salt water fish have been reported for U.S. waters. Uptake of ^{14}C-2,2',4,5,5'-Cl_5-CB by adapted juvenile Atlantic salmon (Salmo salar) is ~3-fold more efficient from freshwater than from seawater (Tulp et al., 1979). The generality of this finding still remains to be proven.

Countries Outside of the United States and Canada. PCBs were first detected in 1967 in fish and wildlife in Great Britain and the Netherlands. PCBs have been found in fish caught in and near Finland in 1982 (Vuorinen et al., 1985), and Norway during 1972-1982 (Skare et al., 1985). Game animals in Spain in 1982-1983 (Hernandez et al., 1985), in West Germany (Brunn et al., 1985) and in Sweden (Villeneuve et al., 1985) have been shown to contain high PCB levels. Birds and animals eating earthworms contaminated with PCBs will accumulate PCBs (Diercxsens, et al., 1985).

Air

Information on the potential inhalation exposure to PCBs is sparse. Even though PCBs exhibit low vapor pressures they have been detected in ambient air, in indoor air and in occupational environments. Samples of ambient air collected using an ethylene-glycol impinger sampler in suburban locations in Florida, Mississippi and Colorado in 1975 contained PCBs at all locations (Kutz and Strassman, 1975).

0.10 μg/m³. Inside laboratories the level was 10 times higher than ambient, averaging 0.21 μg/m³. Comparing outside to inside air of homes on the same day, the levels were 0.004 μg/m³ and 0.31 μg/m³, respectively. In a room containing a burned-out light ballast, PCB levels in air were 50 times higher than normal (11.6 vs. 0.2 μg/m³) for that room and remained elevated for several months afterward. Airborne PCB levels in nine homes ranged from 39-580 ng/m³ with the higher levels occurring in kitchens with pre-1972 fluorescent lighting. Another source of PCB emissions such as video display terminals (VDT) has been reported (Benoit et al., 1984; Digermes and Astrup, 1982) in the foreign literature. Levels ranging from 46-81 ng/m³ were found in offices containing VDTs, whereas the outside air levels were 0.5-1 ng/m³. In three buildings with PCB transformers in Minnesota (Oatman and Roy, 1986) the air levels of Aroclor 1242 and 1254 ranged from 192-881 ng/m³. Surface levels ranged from 0.05-1.47 μg/100 cm². Four buildings without PCB transformers contained air levels ranging from 78-384 ng/m³, and surface levels of 0.05-1.00 μg/100 cm². In another building where improper incineration conditions for Askarel had been used, PCB air levels in 31 buildings ranged from 0.14-3.2 μg/m³ (53 samples) with surface levels ranging from <0.01-4 mg/m² (Thompson et al., 1986).

Since most people spend 16-17 hours/day in buildings (Chapin, 1974), the potential exposure contribution from PCBs in indoor air becomes important relative to outdoors. Because there are few data on PCB levels in indoor air, the total exposure and fractional contribution from indoor air to exposure for humans remains difficult to assess.

Sweden, 1982; Imatra, Finland, 1982; Hallstahammar, Sweden, 1982; in a Swedish locomotive, 1982; Skovda, Sweden, 1982 and Kisa, Sweden, 1983).

Other Exposures

In addition to the occupational exposures and the large exposures characteristic of PCB fires and point-source environmental pollution, the Yusho and Yu-Cheng incidents in Japan (1968) and Taiwan (1979), respectively, have also caused large PCB exposures by ingestion of contaminated rice oil (Hsu et al., 1985; Yoshimura and Hayabuchi, 1985; Chen et al., 1985; Miyata et al., 1985; Kashimoto et al., 1985; Hara, 1985). In Japan, the rice oil samples contained 151-968 ppm Kanechlor 400/500; Yu Cheng oil contained between 22 and 113 ppm (Miyata et al., 1985). The congener contents are known along with the PCQ and PCDF levels. The health effects are dealt with in Chapter VI.

PCB residues as Aroclor 1260 in Louisiana showed PCBs in 1980 from 8 donors to range between 0.59 and 2.33 ppm lipid, and in 1984 from 10 donors to range between 0.65 and 1.96 ppm lipid (Holt et al., 1986). These were among the highest concentrations and occurrences reported by previous U.S. EPA National Human Monitoring Programs. Residues in the breast tissue of females tended to be high. Two hexachlorobiphenyl congeners were determined on autopsy in tissues from seven people who had resided on the Texas Gulf Coast (Ansari et al., 1986). The levels for 2,2',4,4',5,5'-Cl_6-CB in the anterior abdominal wall ranged from 98-276 ppb adipose tissue, <5-251 ppb in the axillary fossae, and 109-231 ppb in the omentum; the levels for 2,2',3,4,4',5 Cl_6-CB in the anterior wall ranged from 211-1625 ppb, <5-1166 in the axillae, and 221-1161 ppb in the omentum. Since fat contents ranged between 7.5 and 20% among the different tissues examined, only fat tetra-CB (6.6%). The corresponding percentages in maternal blood were 8.8, 8.07 and not detected, respectively. While the milk/blood ratio for specific congeners was between 3.5 and 10 for most congeners, the ratio for 2,2,,3',4,4',5-hexa-CB was >7500, and 2,3,3',4,4',5-hexa-CB, 20. Inhalation exposure in the Lake Ontario and the Hudson River areas may also contribute to maternal exposure (2.8±0.5 ng PCB/m^3 (n=6) at Oswego, NY). Safe et al. (1985a) quantitated 80 specific congeners of Aroclor 1260 in a human milk sample and found the 2,4,4'-tri-CB; 2,4,4',5-tetra-CB; 2,2',4,4',5-penta-CB; 2,3',4,4',5-penta-CB; 2,2',3,4,4',5'-hexa-CB; 2,2',4,4',5,5'-hexa-CB; 2,2',3,3',4,4',5'-hepta-CB; and 2,2',3,4,4',5,5'-hepta-CB congeners predominated, unlike in the original formulation.

Similar results (noncorrespondence of abundant congeners in human milk compared with the exposing PCB) have been found in recent studies from Yugoslavia (Krauthacker et al., 1986), Israel (Weisenberg et al., 1985) and Japan (Yakushji et al., 1978; Ando et al., 1985).

Estimated United States Exposure

Table IV-7 presents estimates of the total amount of PCBs potentially received by an adult U.S. male from ambient air, food and drinking water. Seven separate exposure levels for drinking water and three levels for air and food (representing a probable range of exposure levels based on the data presented in the Exposure Estimation section) are shown in the table. The actual contribution of air exposure is not precisely known. Indoor air levels may play an important role in exposure with preliminary findings indicating levels of up to 0.580 μg/m^3 in normal settings such as residential homes. Occupational sources and PCB fires may also contribute to the total exposure. The data presented represent possible exposures based on the occurrence data and the estimated intakes. The values presented in Table IV-7 for air and food levels of PCBs, as well as the values for drinking water levels, represent a range from the values found in the PCB monitoring data (see Drinking Water, Air and Food Sections). The intake from ambient air may be 0.05 μg/kg/day assuming 0.20 μg PCB/m^3 and time-activities of 16 hours indoors. Assuming the intermediate food intake of 0.01 μg/kg/day and the intake of 0.02 μg/kg/day from air to be representative, drinking water would be the predominant source of PCB exposure in the adult male when drinking water levels exceed 1.0 μg/ℓ. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the current data but it is likely that persons in the Hudson River Valley, the Great Lakes Region (except for Lake Superior), the Ohio Valley, the upper Mississippi, and the Cape Fear River in North Carolina have a higher potential for PCB exposures than others.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for PCBs by route of exposure. Eschenroeder et al. (1986) have estimated the possible exposures and the resultant health risk after PCB spills. Since PCBs tend to penetrate down only into the first 2 cm of soil, plants and vegetables with shallow root systems will be predisposed to PCB contamination. As preferential volatilization of the less chlorinated congeners also occurs, the more chlorinated congeners will bioaccumulate.

<u>Summary</u>

The major exposure routes to humans are through food and drinking water, and by inhalation. Dermal exposure is also important in occupational expo-

V. HEALTH EFFECTS IN ANIMALS

Commercial PCB mixtures vary in PCB isomer and congener composition, and impurities. In general, PCB mixtures produce low to moderate acute toxicity in mammalian species, but produce pronounced subacute and chronic toxicity. In contrast, invertebrates exhibit greater acute toxicity to PCBs (LC_{50}s <1 mg/ℓ) (NAS, 1979). In addition, as reported for other halogenated aromatic hydrocarbons, PCBs exhibit significant interspecies variability in toxicity. In considering the health effects of PCBs in animals, it is important to consider the isomer and congener composition of the PCBs, potential impurities, the length of exposure and the species under investigation.

Acute Toxicity

Representative toxicity data following a single exposure to PCBs are summarized in Table V-1. Single oral dose LD_{50}s of commercial PCB mixtures in rats ranged from 1.01-11.3 g/kg bw (see Table V-1). The data do not establish a consistent relationship between commercial PCB formulations and reported LD_{50}s. Some of the variability in reported LD_{50}s for specific PCB mixtures has been related to differences in the observation period, strain and solute concentrations. There appears to be no significant sex differences in the acute toxicity for the PCB mixtures studied; however, Aroclor 1254 was found to be slightly more toxic to immature than mature rats (Linder et al, 1974; Grant and Phillips 1974).

TABLE V-1 (cont.)

Species/ Strain	Sex/No.	Source of PCB	Route	LD_{50}	Comments	Reference
Rat/NR	NR	Aroclor 1221	oral	3.98 g/kg bw	Toxicity apparently decreasing with increasing chlorine substitution	Fishbein, 1974; Nelson et al., 1972
		Aroclor 1232	oral	4.47 g/kg bw		
		Aroclor 1242	oral	8.65 g/kg bw		
		Aroclor 1248	oral	11 g/kg bw		
		Aroclor 1260	oral	10 g/kg bw		
		Aroclor 1262	oral	11.3 g/kg bw		
		Aroclor 1268	oral	10.9 g/kg bw		
Rat/Sherman	F/NR	Aroclor 1221	oral	4.0 g/kg bw		Nelson et al., 1972
		Aroclor 1262	oral	11.3 g/kg bw		
Rat/Osborne-Mendel	M/NR	Aroclor 1254	oral	1.01 g/kg bw	Single observation period	Garthoff et al., 1981
	M/NR	Aroclor 1254	oral	1.53 g/kg bw	5 multiple doses 2 times/week	
	M/NR	Aroclor 1254	oral	1.99 g/kg bw	5 multiple doses 1 time/week	
Rabbit/NR		Aroclor 1221	dermal	2.000-3.169 g/kg bw		Nelson et al., 1972
		Aroclor 1232	dermal	1.26-2.0 g/kg bw		
		Aroclor 1242	dermal	0.794-1.269 g/kg bw		
		Aroclor 1248	dermal	0.794-1.269 g/kg bw		
		Aroclor 1260	dermal	1.26-2.0 g/kg bw		
		Aroclor 1262	dermal	1.26-3.16 g/kg bw		
		Aroclor 1268	dermal	2.5 g/kg bw		
Rabbits	NR	NR	NR	8-11 g/kg bw		Peakall, 1975
Mice/CFI	M/NR	Kanechlor 400	oral	1.875 mℓ/kg bw		Kimbrough et al., 1978
Mice/CFI	F/NR	Kanechlor 400	oral	1.57 mℓ/kg bw		
Mice/dd	F/NR	2',4'-di-CB	oral	7.86 g/kg bw	Data reviewed suggest increased toxicity in mice with greater chlorine substitution	Kimbrough et al., 1978
Mice/DVI	NR	tri-CB	oral	3.06-4.25 g/kg bw		
Mice/DVI	NR	2,4,3',4'-tetra-CB	i.p.	2.15 g/kg bw		
Mice/CFI	NR	2,3,4,3',4'-penta-CB	i.p.	0.65 g/kg bw		

LD_{50} values from dermal application of commercial PCB mixtures in rabbits ranged from 0.794-3.169 g/kg (see Table V-1). There was no association of degree of toxicity with chlorine content. In addition, the data suggest that PCBs are readily absorbed following dermal exposure, although no comparative data are available on toxicity in rabbits following oral exposure. Several reviews (Peakall, 1972; Nelson et al., 1972; Fishbein, 1974; Kimbrough, 1974; NIOSH, 1977; Kimbrough et al., 1978; McConnell, 1980a) report both LD_{50} data and a further discussion of the acute toxic effects of PCBs.

As mentioned previously, the toxicity of PCB mixtures can vary because of a number of factors, including the content of specific congeners and isomers. Kimbrough et al. (1978) reported increased toxicity in mice exposed to PCB congeners containing greater chlorine substitution. The structural requirements for biological activity (AHH induction) and toxicity of this class of compounds has been recently reviewed (Poland and Knutson, 1982). One of the structure requirements for AHH induction, and apparently toxicity, is an unsubstituted carbon atom in the ortho position. These PCB congeners produce biologic and toxic activities related to that produced by chlorinated dibenzodioxins and dibenzofurans. 3,3',4,4'-tetra-CB and 3,3',4,4',5,5'-hexa-CB (Biocca et al., 1976; McKinney, 1976) and 3,3',4,4',5-penta-CB (Safe, 1984) are highly toxic. The 3,3',4,4'-tetra-CB is found in commercial PCB mixtures (Albro and Parker, 1979).

Subchronic Toxicity

Multiple exposure studies are summarized by species and route of exposure in Tables V-2 to V-5. As with acute toxicity, attention must be given to the type of PCB, species, and the route of exposure employed in

TABLE V-2 (cont.)

Strain	Sex/No.	Weight/Age	Source of PCBs/Vehicle	Dose/Duration	Animal Effects	References
Sprague-Dawley	M,F/48	adult and 35 days	Phenoclor DP6/diet	13 ppm adult 24 ppm young for 8 days	Liver weight elevated equally in both sexes; elevated liver protein and fat more noticeable in adults.	Narbonne, 1979
Fischer	M/50	34 days	Aroclor 1254/diet	0, 20 ppm for 1, 2, 4, 8, or 14 days	Hepatomegaly by day 4.	Carter, 1983
CD	F/3/group		4-mono-CB/cottonseed oil	30 mg/kg bw/day on days 8, 11, 13, 15, 18 of pregnancy	Elevated intestinal monoamine oxidase, serum sorbitol dehydrogenase and alkaline phosphatase.	Wolden et al., 1982
Long-Evans	M/12	130 g	Aroclor 1248/diet	0 or 100 ppm for 4 weeks	Hepatomegaly (4.46% of bw), obvious increase in SER.	Allen et al., 1975
			2,5,2',5'-tetra-CB		Hepatomegaly (3.38% of bw), less obvious increase in SER.	
Wistar	M,F/38	NR	Aroclor 1254/diet	1000 ppm for 14 or 30 days	At ≥14 days, 30-72% reduction in rate of gain; at 30 days, 29% reduction in food intake; no change in liver weight. Altered cholesterol, fatty acid synthesis.	Kling et al., 1978
Osborne-Mendel	M/6/group	8 weeks	Aroclor 1254/diet	0, 5, 50, 500 ppm for 4 weeks	≥5 ppm: enlarged thyroid, reduced follicle size, follicular lumen reduced, papillary projections and cytoplasmic projections, diluted RER.	Collins and Capen, 1980b
Gunn	M/12/group	300-400 g	Aroclor 1254/diet	500 ppm for 42 days	Thyroid follicular cells more columnar, diluted RER, vacuolated mitochondria.	Collins and Capen, 1980a
Osborne-Mendel	M/NR	8 weeks	Aroclor 1254/diet	0, 50, 500 ppm for 4 or 12 weeks	≥50 ppm, by 4 weeks: enlarged thyroid, follicular cells more columnar, vacuoled cytoplasm, papillary projections, cytoplasmic processes. Dilated RER, Golgi apparatus more prominent, larger number of enlarged lysosomes. Reduced serum thyroxin; after 35-week recovery period thyroids resemble those of controls, serum thyroxin normal.	Collins et al., 1977

TABLE V-2 (cont.)

Strain	Sex/No.	Weight/Age	Source of PCBs/Vehicle	Dose/Duration	Animal Effects	References
Sprague-Dawley	M/NR	100 g	Aroclor 1248, 1254 or 1260/diet	0 or 1000 ppm up to 6 weeks	Reduced rate of gain: Aroclor 1248 > 1254 > 1260. Moderate elevation of Hb, PCV. Relative neutrophilia, lymphocytopenia. Enlarged liver, decreased thymus, fatty liver degenerations, cystic areas and focal necrosis with infiltration of inflammatory cells. ER proliferation, vesiculation of RER, increased number of lysozymes. Increased hepatic protein, RNA, phospholipid; decreased DNA, cholesterol. Induction of N-demethylase, nitroreductase.	Allen and Abrahamson, 1973
Wistar	F/8	112-130 g	Phenoclor DD6/diet	2000 ppm up to 56 days	>3 weeks, UV fluorescence of incisors, small intestine (porphyria). Hepatic enlargement with centrilobular degeneration. Splenic degeneration with disappearance of white pulp, reduction in red pulp, evidence of siderosis.	Vos and Koeman, 1970
Sprague-Dawley	M,F/4/group	NR	Clophen A-50/olive oil	0 or 100 mg/kg bw 1 time/week for 7 weeks	M: Increased liver percent of bw from 2.6-3.3%. Presence of ATPase deficient islands. F: Increased liver percent of bw from 2.9-3.6%. Greater presence of ATPase deficient islands.	Deml and Oesterle, 1982
Holtzman	M/30	NR	Aroclor 1254/diet	0, 5, 50, 500 ppm for 5 weeks	$\geq$50 ppm: hepatomegaly, fatty degeneration, hepatocellular hypertrophy and cytoplasmic vacuolization. $\geq$5 ppm: enlarged SER; decreased number of mitochondria, lysosomes; increased Golgi apparatus. $\geq$50 ppm: Golgi apparatus decreased.	Kasza et al., 1978b
Holtzman	M/30	NR	Aroclor 1254/diet	0, 5, 50 or 500 ppm for 5 weeks	$\geq$5 ppm: enlarged thyroid, reduction in follicular size, hyperplastic cells with papillae and cytoplasmic processes extending into lumenal colloid; follicular cells more columnar, mitochondria vacuolated with disrupted cristae, accumulation of colloid, increased number of lysosomes.	Kasza et al., 1978a

NR = Not reported

TABLE V-3 (cont.)

Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects			Reference
						Lowest exposure (ppm) to cause:			
						Enlarged Liver	Reduced Spleen Thymus Wt.	Increased Testis Weight	Biocca et al., 1981
C57Bl/6J	M/5/group	18-20 g, 5 weeks	3,4,5-sym. hexa-CB...	diet	0, 0.3, 1, 3, 10 or 30 ppm diet for 28 days	...0.3	10	10	
			2,4,6-sym. hexa-CB...			...100	300	NR	
			2,4,5-sym. hexa-CB...			... 30	300	NR	
			2,3,6-sym. hexa-CB...		0, 10, 30, 100 or 300 ppm diet for 28 days	... NR	NR	NR	
						300 ppm Diet	Levels in Adipose	Levels in Liver	
						3,4,5-	6912	1344	
						2,4,6-	4329	1022	
						2,4,5-	3923	637	
						2,3,6-	280	52	
						30 ppm 3,4,5-hexa-CB depressed serum protein, caused UV fluorescence of liver, teeth, sternum. Liver: 1.0 ppm 3,4,5-hexa-CB caused liver microabscesses to severe fatty degeneration and necrosis at 30 ppm. Other isomers: same lesions at 300 ppm. Thymus: 3.0 ppm 3,4,5-hexa-CB caused moderate to marked involution at 30 ppm; 300 ppm 2,4,6-hexa-CB caused marked involution; 300 ppm 2,3,6-hexa-CB caused slight involution. Spleen: 3.0-30 ppm 3,4,5-hexa-CB, 300 ppm 2,4,6-hexa-CB caused moderate depletion of lymphocytes. 3,4,5-hexa-CB: enlarged spermatagonia. 2,4,6-hexa-CB: cardiomyopathy and passive congestion of liver, lung.			
BALB/CJ	M/~13/group	18-20 g	Aroclor 1242	diet	0 or 167 ppm for 6 weeks	Increased ($p<0.05$) mortality caused by _Salmonella typhosa_ endotoxin at 6 weeks. Increased ($p<0.05$) mortality caused by _Plasmodium berghei_ at 3 weeks. Hepatocytic hypertrophy; no histological alteration of lymphoid tissues.			Loose et al., 1978b

TABLE V-4

Acute, Short-term and Subchronic Toxicity of PCBs Administered by Routes Other Than Oral

Route	Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	References
s.c.	Guinea pig/ NR	NR/54	NR	NR; 42% Cl	None	69-690 mg, single dose	Local injection necrosis to fibrous encapsulation. Hepatic: centrilobular necrosis, atrophy; fatty infiltration, splenic lymphoid hyperplasia, pulmonary congestion, mortality.	Miller, 1944
s.c.	Guinea pig/ NR	NR/10	NR	NR; ~42% Cl	Mineral oil	345 mg, single dose	As above; complete mortality 13 days; pulmonary congestion more severe	
s.c.	Rat/NR	NR/30	NR	NR; ~42% Cl	None	69 or 690 mg, single dose	Fatty liver degeneration; splenic hypertrophy; local injection fibrous encapsulation	
s.c.	Rabbit/NR	NR/3	NR	NR; ~42% Cl	None	690 or 1380 mg, single dose	Death in 14-72 days (as above, except liver contained fine droplets of fat).	
		NR/3	NR	NR; ~42% Cl	Mineral oil	345 or 690 mg, single dose	Death in 42-360 days (as above, except liver contained fine droplets of fat).	
Dermal	Guinea pig/ NR	NR/11	NR	NR; ~42% Cl	None	34.5 mg/day for 11 days	Death within 21 days. (Dermal epithelial destruction. Lesions in internal organs as above.)	
		NR/16	NR	NR; ~42% Cl	Mineral oil	3.5-17 mg/day for 7 or 15 days		
s.c.	Mice/ddY	F/NR	7-8 weeks	Kanechlor 500	95% ethanol	0-10 mg/day for 10 days	Killed 2 days after last dose: Mortality ≥ 4 mg/day	Watanabe and Sugahara, 1981
i.p.	Rat/NR	M/NR	NR	Aroclor 1254	NR	100 mg/kg/ day for 6 days	Aminolevulinic acid (ALA) synthetase activity increased, ALA dehydratase activity decreased, microsomal heme and cytochrome P-450 increased	
Inhalation	Rat/NR	M/5, F/5	NR	Decachlorobiphenyl	NA	2.54 g/m³ for 6 hours	Blinking and sneezing, reversible; 14-day observation, no effects on appetite or growth. Gross pathology, no lesions.	Berczy et al., 1974

TABLE V-4 (cont.)

Route	Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	References
i.p.	Rat/Sprague-Dawley	M/13	NR	Aroclor 1242	Peanut oil	100 mg/kg bw twice weekly for 6 weeks, once weekly for an additional 4 weeks	Body weight loss, hepatic midzonal sudanophilic vacuolization, focal necrosis, dilation of renal tubules with proteinaceous casts. Decreased PCV, RBC, hemoglobin, neutrophia. Increased serum iron, decreased corticosteroids and blood glucose. Increased urinary protein sugar, coproporphyrin.	Bruckner et al., 1974b
i.p.	Rat/Sprague Dawley	M/24	200-300 g	Aroclor 1242	Peanut oil	0, 1, 5, 25, 50 or 100 mg/kg bw,	Elevated hydroxylation, N-demethylation, cytochrome P-450	Bruckner et al., 1974b
		M/6/treated group, 3/control group	NR	Aroclor 1242	Peanut oil	single dose 0 or 100 mg/kg bw, single dose	Examinations of microsomal enzyme induction at 1, 5, 10, 20, 40 days post-treatment indicated maximum induction at 5 days, some residual induction at 20 days. Hydroxylation most dramatically elevated.	
i.p.	Rat/Wistar	M/120	250 g	Clophen A-50	Corn oil	0 or 100 mg/kg bw, single dose 4 weeks observation	Cytochrome P-450 increased 3- to 4-fold, maximum in 1 week. NADPH activity doubled, P-nitroanisole O-demethylase induced 6- to 7-fold; ~4-fold after 1 month. AHH activity increased 3-fold, down to normal ~1 month. Microsomal epoxide hydratase increased 2.5-fold at 1 week, persisted at least 4 weeks. Glutathione S-transferase increased at 1 day remained at these levels. Microsomal UDP glucuronosyltransferase activity increased 2.5-fold in 1 week, persisted 4 weeks.	Parkki et al., 1977
i.p.	Mice/BALB/CJ	NR/4-10/group	NR	Aroclor 1242	Corn oil	1000 mg/kg bw single dose	Splenomegaly: significant by day 6, peak by day 9, gone by day 13. Cellularity: significant reduction in lymphocytes days 6-10.	Carter and Clancey, 1980

TABLE V-5

Acute, Short-term and Subchronic Toxicity of Orally-Administered PCBs to Other Species

Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	Reference
Monkey/ rhesus	M/7	9.2 kg/ adult	2,5,2',5'-tetra-CB	corn oil	0.18 mg/kg bw	Moderate proliferation of SER, slight decrease of liver DNA, increase in cytochrome P-450.	Allen et al., 1975
Rabbit/ New Zealand White	F/20, M/20	NR	Aroclor 1221, Aroclor 1242 Aroclor 1254	corn oil	0 or 300 mg 1 time weekly for 14 weeks	Aroclor 1242, 1254: elevated SGOT, SGPT. Aroclor 1254: slight transient increase in serum cholesterol, reduced rate of gain, severe hepatomegaly, uterine atrophy. No differences in hematologic parameters, BUN, serum protein fractions. Histopathology, Aroclor 1254: vacuolated and granular enlarged hepatocytes, centrilobular necrosis and fibrosis. Ballooned RER. Lesions less obvious in Aroclor 1242-exposed, absent in Aroclor 1221-exposed.	Koller and Zinkl, 1973
Rabbit/NR	F/16	adult	Aroclor 1254	corn oil	0, 1.0, 10, 12.5, 25, 50 mg/kg bw daily for 28 days	No effect on total number of fetuses, number of viable fetuses, number of resorption sites or number of abortions at doses of 1.0 or 10 mg/kg bw/day. Liver weights in the dams were significantly increased at the 10 mg/kg bw/day dose. Effects on fetal viability as well as other maternal effects were seen at doses of 12.5 or greater.	Villeneuve et al., 1971a,b
Rabbit/New Zealand White	M/7/group	~2 kg	Aroclor 1254	diet	0, 3.7, 20.0, 45.8, 170 ppm diet for 8 weeks: 0.18, 0.92, 2.1 or 6.54 mg/kg bw/day, respectively	No effect on feed consumption, growth rate, visceral pathology except hepatomegaly which was statistically significant (p=0.05) at the highest two doses. No effect on hematologic parameters. No consistent immunological response (hemolysis or hemagglutination titers) to sheep RBC. Gamma globulin reduced at all levels. No effect on dermal tuberculin reaction. Splenic and thymic reductions in gamma globulin-producing cells, dose-related.	Street and Sharma, 1975
Guinea pig/ Dunbar/ Hartley	F/5-19/ group	500-600 g/ 8-10 weeks	Clophen A50 2,4,5,2',4',5'-hexa-CB	peanut oil	25 or 100 mg. Total doses over 55 days	"All seemed unaffected by the treatment." Clophen A-50: increased cytochrome P-450	Brunstroem et al., 1982

TABLE V-5 (cont.)

Species/ Strain	Sex/No.	Weight/Age	Source of PCBs	Vehicle	Dose/Duration	Animal Effects	Reference
Monkey/ rhesus	M/7	9.2 kg/adult	2,5,2',5'-tetra-CB	corn oil	0 or 18 mg/kg bw, single dose	"No obvious clinical effects." No change in hematology. Levels (14 days) of tetra-CB: adiposa, 135; adrenals, 33; lung and heart, 9; liver and skin, 4; thyroid, 2 μg/g tissue. Microscopically, all tissues normal. Hepatic ultrastructive: proliferation of SER, elevated cytochrome P-450.	Allen et al., 1975
Monkey/ rhesus	NR	adult	Aroclor 1248	diet	100 or 300 ppm for 2-3 months	Gradual weight loss, alopecia lacrimations, conjunctival congestion, facial edema, comedones, large intrafollicular keratin cysts. Hematology: gradual decrease in PCV, Hb; lymphocytopenia and concomitant neutrophilia. Reduced serum proteins, lipids, cholesterol, triglycerides. Thickened gastric mucosa with mucin-filled cysts, moderately invasive gastric hyperplasia. Two-fold hepatomegaly, enlarged hepatocytes with increased SER; decreased liver DNA, RNA, increased MFO.	Allen, 1975
Monkey/ rhesus	M/2 F/2	2.8-3.6 kg	2,5,4'-triCB	diet	5 ppm for 84 days (historic controls)	Most organs: increased blood volume. Increased relative liver, brain weight (males). Microscopically, venous congestion in many tissues. Adrenals: hemorrhages and cellular changes in zona fasciculata. Renal cortical and medulary degeneration, tubal colloid. Liver: congestion, fatty infiltrations. CNS: parenchymal and mesenchymal degeneration, macrozlial proliferation, gliosis, swelling of Purkinje cells.	Iatropoulos et al., 1977

NR = Not reported

Additional hepatic alterations were described by Kasza et al. (1978b). Four-week-old male Holtzman rats received 0, 5, 50 or 500 mg Aroclor 1254/kg in the diet for 5 weeks. The animals experienced hepatic alterations consistent with those previously described in this section. Additionally, a dose-related increase in the number of liposomes, as well as lipid droplets and an increase in the number of Golgi apparatus at the 5 ppm exposure level and a modest reduction in Golgi apparatus in the 50 and 500 ppm exposed groups. Laminated cytoplasmic inclusions or membrane whorls were seen in hepatocytes from rats exposed to 500 ppm. The observations from this study indicate that a blockage occurred in the mechanism by which hepatocytes discharge lipids.

PCBs have been used widely to induce hepatic enzymes, often in studies with other chemicals. In these studies, large doses of PCBs are often given by i.p. injection or gavage to obtain maximal enzyme induction.

The rapidity in which certain hepatic enzyme activities are induced and their persistence in the induced form was demonstrated in a study by Parkki et al. (1977). A one-time i.p. administration of 100 mg Clophen A-50/kg bw to male Wistar rats elicited profound biochemical changes in the liver. Cytochrome P-450 levels increased 3- to 4-fold with a maximum achieved in 1 week. NADPH cytochrome c reductase activity doubled, and p-nitroanisole-o-demethylase activity increased 6- to 7-fold and declined to ~4 times normal activity at the end of the 4-week observation period. AHH activity increased 3-fold initially and had returned to normal by the end of 4 weeks. Microsomal epoxide hydratase activity had increased 2.5-fold at 1 week and persisted at this level. Glutathione-S-transferase activity had increased by 1 day and remained elevated for 4 weeks.

microabscesses were found at doses $\geq$1.0 ppm of diet (Biocca et al., 1981). This study used groups of five C57Bl/6J male mice to test the relative potency of four symmetrical isomers of hexa-CB. The other isomers tested elicited similar responses at the 30-300 ppm diet level. Mattson et al. (1981) observed hepatomegaly in groups of female CBA mice that were exposed to 2,2',4,4',5,5'-hexa-CB in peanut oil at levels of 0.5 mg/mouse/ day for 7 days. Higher levels of commercially available PCB products are necessary to elicit these hepatic responses. Loose et al. (1978b) exposed groups of male/BALB/CJ mice to a diet containing 167 ppm Aroclor 1242 for 6 weeks to demonstrate hepatocytic hypertrophy. Sanders et al. (1974) demonstrated hepatomegaly in groups of five adult male ICR mice exposed to dietary levels of 250 ppm Aroclor 1254 for 14 days.

Other species have demonstrated variable alterations in hepatic parameters upon exposure to PCBs. Oral administration of levels as low as 3.7 ppm Aroclor 1254 in the diet (0.18 mg/kg bw/day) for 8 weeks to male New Zealand rabbits failed to produced hepatomegaly (Street and Sharma, 1975). Guinea pigs treated with a 250 mg Clophen A-60/kg diet for 4-7 weeks experienced hepatomegaly with "liver damage" (Vos and van Genderen, 1973).

Skin -- Only one study was found that implicated PCBs (Aroclor 1254) in dermatitis in rats (Zinkl, 1977). Alopecia and a crusty dermatitis with serum ooze developed first on the ears, then the dorsum of the nose, tail and feet of female CD rats after 10 weeks of exposure to 100 ppm Aroclor 1254 diet.

Signs of toxicity in monkeys acutely exposed to PCBs closely parallel those reported in other species with a few notable exceptions. Frequently, endotoxin and _Plasmodium berghei_ in groups of male BALB/CJ mice that were treated with 167 ppm Aroclor 1016 or 1242 in the diet for 6 weeks. These treatments did not result in histologically-demonstrable lesions in thymus, spleen or mesenteric lymph nodes. Thomas and Hinsdill (1978) demonstrated decreased mortality of _S. typhimurium_ in groups of outbred female mice that were given 1000 ppm Aroclor 1248 in the diet for 5 weeks and an apparent dose-related increase in mortality caused by _S. typhimurium_ endotoxin at levels of 100 and 1000 mg/kg diet.

Male C57Bl/6J mice exposed to one of four symmetrical hexa-CB isomers exhibited thymic involution especially with 3,3',4,4',5,5'-hexa-CB. Concentrations of 3.0 ppm in the diet for 28 days caused moderate depletion of splenic lymphocytes (Biocca et al., 1981).

The guinea pig demonstrated immunosuppression resulting from a 4- to 7-week exposure of groups of female albino guinea pigs to 50 ppm of Clophen A-60 or Aroclor 1260 in the diet (Vos and de Roij, 1972; Vos and van Genderen, 1973). In this same laboratory, guinea pigs were exposed to ≤250 ppm of Clophen A-60 in the diet for 4-7 weeks experienced atrophy of lymphoid tissue and reduction in tetanus antitoxin titers following injection with tetanus toxoid (Vos and van Genderen, 1973). However, recently Brunstroem et al. (1982) reported that all animals "seemed unaffected by the treatment" in a study that exposed pregnant females to total Clophen A-50 or 2,2',4,4',5,5'-hexa-CB amounts of 100 mg over a 55-day period.

Dermal applications of 120 mg of either 2,2',4,4',5,5'-hexa-CB or Aroclor 1260, 5 times weekly for 4 weeks resulted in moderate thymic atrophy in rabbits (Vos and Notenboom-Ram, 1972), the most severe of which was promg Aroclor 1254/kg bw for 7 days resulted in increased acid phosphatase activity in testicular interstitial cells (Dikshith et al., 1975). These studies indicate that PCBs may indirectly hasten steroid catabolism (Spencer, 1982).

<u>Gastrointestinal System</u> -- Development of gastritis progressing to a moderately invasive gastric hyperplasia in the individuals were described in the rhesus monkeys after consuming ~260 mg Aroclor 1248 over 2 months (Allen et al., 1974b) and in six male monkeys exposed for 3 months to a diet containing 300 mg Aroclor 1248 diet (Allen and Norback, 1973). Upon necropsy, edematous thickening of the stomach wall accompanied by glandular hyperplasia was observed. Glandular cells accumulated mucus, resulting in the formation of large, mucus containing cysts. Alterations of the glandular epithelial cells and their nuclei accompanied by inflammatory processes and invasion of the muscularis were observed.

<u>Urinary System</u> -- Rabbits exposed to PCBs responded in a manner similar to other species (Villeneuve et al., 1971a,b) with the exception that dermal application of any of three commercially available PCB products resulted in severe renal damage (Vos and Beems, 1971). Applied at 118 mg, 5 times weekly for 27 applications (38 days), Phenoclor DP6, Clophen A-60 and Aroclor 1260 all resulted in hydropic degeneration of convoluted tubules, destruction of tubular epithelial cells with resultant tubular dilatation and proteinaceous casts. No mention of such lesions was made in a subsequent study by this laboratory using a total of 20 such applications (Vos and Notenboom-Ram, 1972).

the diet fed for 2 weeks to groups of male 250 g Holtzman rats (Garthoff et al., 1977). Baumann et al. (1983) found increased levels of urinary porphyrin and porphyrin precursors in groups of ten 100 g male Wistar/Neuherberg rats following treatment by gavage with 50 mg Clophen A-50/kg bw for 6 weeks.

Iatropoulos et al. (1977) exposed male and female rhesus monkeys to 5 ppm of 2,4',5-tri-CB diet for 84 days. No mention of total PCB intake was made. They reported a generalized increased blood volume of many tissues apparently resulting from dilation of arterioles, capillaries and veins. Hemorrhages and cellular changes in the adrenal cortex were observed. Parenchymal and mesenchymal degeneration in the brain was also reported.

Chronic Toxicity

Chronic toxicity studies discussed in this section include those >90 days in duration. These studies are summarized in Tables V-6 to V-9.

In contrast to acute toxicity induced by commercial mixtures of PCBs, chronic studies clearly indicate differences in the relative toxicity of the commercial PCB mixtures. A 14-week oral exposure (300 mg, once a week) study evaluated the relative toxicity of Aroclor 1221, 1242 and 1254 in rabbits and found that Aroclor 1254 was the most toxic and that Aroclor 1221 was the least toxic of the products tested (Koller and Zinkl, 1973). Similarly, male BALB/CJ mice fed diets containing Aroclors 1221, 1242 or 1254 resulted in the determination that Aroclor 1254 was more toxic than Aroclors 1242 and 1221 (Koller, 1977).

TABLE V-6 (cont.)

Strain	Sex/No.	Source of PCB	Vehicle	Dosage Schedule	Duration of Study	Animal Effects	Reference
Sprague-Dawley	F/6/group	Aroclor 1242	diet	0, 75 or 150 ppm for 8 or 36 weeks	36 weeks	Both levels: massive venous engorgement of liver with characteristic darkening; marked focal neurosis and regeneration, enlarged hepatocytes; many mitoses and multinucleate cells, accumulation of pigment adjacent to veins, heaviest in Kupfer cells; accumulation of lipid droplets in cytoplasm, some with areas suggestive of lipid-cholesterol complexes; marked SER proliferation; deposits of iron; granular degeneration of mitochondria; many hepatocytes contained whorl-like membranous bodies.	Jonsson et al., 1981
Sherman	M/10, F/10 per group	Aroclor 1254	diet	0, 20, 100, 500 ppm for 8 months	8 months	Mortality (3/20) and reduced rate of gain at 500 ppm. Hepatomegaly, enlarged hepatocytes with foamy cytoplasm-containing inclusions at $\geq$20 ppm. Adenofibrosis and pigment accumulation at $\geq$100 ppm.	Kimbrough et al., 1972
	M/10, F/10 per group	Aroclor 1260	diet	0, 20, 100, 500, 1000 ppm for 8 months	8 months	Mortality 1/10, 2/10, 8/10 of females in 100, 500, 1000 ppm groups. Decreased rate of gain at $\geq$500 ppm. Hepatomegaly, male and female at $\geq$20 ppm, discolored livers with UV fluorescence, enlarged hepatocytes with foamy cytoplasm-containing inclusions. Increased lipid content at $\geq$100 ppm. Pigment accumulations at 500 ppm. Adenofibrosis at $\geq$100 ppm.	
Sprague-Dawley	M/96	Aroclor 1248, Aroclor 1254 or Aroclor 1262	diet	0 or 100 ppm for 52 weeks	65 weeks	Normal appetites, appearance, weight gain, Hb, PCV, WBC, serum protein, A/G ratios. Elevated serum total lipids, cholesterol. Total lipid and triglyceride spiked very high peaks on Aroclor 1254 (only) at 52 weeks. Cholesterol levels persisted at 65 weeks (13 weeks off exposure). Triglyceride levels fell less than controls by 65 weeks. Hepatomegaly: focal degeneration and necrosis by 13 weeks.	Allen et al., 1976

TABLE V-8

Effects of Chronic Exposure of Monkeys to PCBs

Strain	Sex/No.	Source of PCBs	Vehicle	Dosage	Duration of Study	Animal Effects	Reference
Rhesus	F/24 M/NR	Aroclor 1248	diet	0, 2.5 or 5.0 ppm for ~18 months	~39.6 months	Males (5.0 ppm level only): moderate erythema and periorbital edema. Females: more severe skin lesions (alopecia, acne); extreme weight loss, irregular menstrual cycle length, depressed serum progesterone. Considerable improvement after 1-year recovery period.	Barsotti and Allen, 1975
Rhesus	F/30	Aroclor 1248	diet	0, 2.5 or 5.0 ppm	~16 months Total intake 90 or 180 ppm by females in 6 months	Skin lesions as above; 15% weight loss in females. Normal hematograms. After 6 months: serum total lipids reduced, shift in A/G ratio, elevated SGPT. Menstrual cycles lengthened. Serum progesterone and estradiol reduced. After 12 months, serum cholesterol and triglyceride reduced.	Barsotti, et al., 1976; Allen et al., 1979b;
	M/10	Aroclor 1248	diet	0 or 5.0 ppm for ~16 months			
	F/8/group	Aroclor 1248	diet	0.5 or 1.0 ppm 3 times weekly for ~16.6 months	~16.6 months Total intake ~8 or 16 mg after 7 months	No irregularities in menstrual cycle, or serum estradiol, progesterone or reproduction success. Infants smaller, skin hyperpigmentated.	
	F/24	Aroclor 1016	diet	0.025, 0.25 or 1.0 ppm	NR	No abnormalities of clinical, gross or reproductive parameters in adults. 1.0 ppm: Infants born in the 1.0 ppm group were significantly smaller than controls.	Barsotti and van Miller, 1984
Rhesus	NR/7	Aroclor 1248	transplacental or mother's milk	Mothers exposed to PCBs 6 months before to gestation through gestation and 3-4 months of nursing	Up to infant age of 24 months	Significantly increased locomotor behavior (hyperactivity). Significantly retarded learning ability.	Bowman et al., 1978, 1981
		Aroclor 1248	transplacental or mother's milk	Mothers removed from exposure to PCBs for 22-84 weeks before conception		Mothers exposed to ≥2.5 mg/kg: hyperactivity.	

TABLE V-8 (cont.)

Strain	Sex/No.	Source of PCBs	Vehicle	Dosage	Duration of Study	Animal Effects	Reference
Rhesus	M/6	"PCB"	salad oil in banana	0 or 0.5 mg/kg bw (79.2-253.6 mg)	Up to 5 months	Symptoms of all treated animals similar: 17.3% weight loss, partial alopecia, palpebral edema, acneform eruptions, squamous metaplasia of meibomian glands.	Ohnishi and Kohno, 1979
	F/6	"PCB with PCDF"	diet	2.5 ppm bw PCDF			

[a]P-KC-400 = Kanechlor 400 with PCDFs removed

[b]Y-PCB was prepared from Kanechlor 400, contained ~400 ppm PCDFs

[c]PY-PCB = Y-PCB with PCDFs removed

NA = Not available

It is readily apparent that the toxicity of PCB congeners is dependent on the degree and positioning of chlorine on the biphenyl molecule. From a 5 week exposure study Biocca et al. (1981) determined the toxic potential of various hexachlorinated biphenyl isomers in mice and ranked them relative to their toxic potency: 3,4,5-sym-hexa-CB >> 2,4,6-sym-hexa-CB > 2,4,5-sym-hexa-CB > 2,3,6-sym-hexa-CB. Biocca et al. (1981) also reported the same ranking for the relative persistence of the hexa-CB isomers, with 3,4,5-sym-hexa-CB having the highest levels in adipose tissue and liver. Another example of a structure-toxicity relationship for PCBs is reported in the study by McNulty et al. (1980). Administration of a diet containing 0.3-3.0 ppm 3,3',4,4'-tetra-CB caused chloracne, weight loss and death in rhesus monkeys in 1-6 months, while similar feeding of 2,2',5,5'-tetra-CB produced no clinical or pathologic lesions. Toxicity appears to be related to the ability of the congener to bind to a receptor and initiate subsequent genetic expression resulting in pleiotrophic responses (Poland and Knutson, 1982).

Species differences in sensitivity to PCB toxicity have been identified in chronic exposure studies. The monkey appears to be more sensitive to PCBs than rodents. Sprague-Dawley rats did not exhibit excessive mortality when exposed to 100 ppm dietary levels of Aroclor 1248 for 65 weeks; however, rhesus monkeys fed diets containing 25, 5 and 2.5 ppm produced morbidity and mortality after consuming these diets for 2 months and $\leq$18 months, respectively (Allen and Abrahamson, 1979; Allen et al., 1974b; Barsotti et al., 1976). In addition, the mink appears to be one of the more susceptible species to PCB toxicity. Studies have shown that as little as 2 ppm Aroclor 1254 in the diet for 10 months resulted in complete reproductive failure (Aulerich and Ringer, 1977). A subsequent study indicated that the mink was occurred with dietary exposure to these commercial PCB mixtures. Both studies confirmed that the enlargement in livers of PCB-exposed animals was in part due to hypertrophy of individual hepatocytes. Other findings included focal necrosis, hepatocytic regeneration, mitoses and multinucleate cells, cytoplasmic vacuolization and iron deposits in perivascular macrophages, Kupfer cells and hepatocytes.

Ito et al. (1973) exposed male dd mice for 32 weeks to 100, 250 or 500 ppm Kanechlor 300, 400 or 500 in the diet. They reported hepatomegaly, oval cell formation and bile duct proliferation with increasing incidence apparently related to the degree of chlorination of the Kanechlors. Amyloidosis occurred with a greater incidence when smaller doses of less heavily chlorinated Kanechlors were fed in the diet. Kimbrough and Linder (1974) reported hepatopathology in male BALB/CJ mice fed 300 ppm Aroclor 1254 in the diet for 6 or 11 months but made no mention of amyloidosis.

Exposure of animals to pure PCB congeners elicited similar signs of hepatotoxicity. The 2,4,5,2',4',5'-hexa-CB; 2,4,6,2',4',6'-hexa-CB; 2,3,5,2',3',5'-hexa-CB and 2,3,4,5,2',3',4',5'-octa-CB congeners produced alterations in rat livers detectable by conventional histopathological procedures; these included hepatocytes with vacuolated cytoplasm and focal necrosis (Hansell and Ecobichon, 1974).

Hypertrophy of individual hepatocytes has been shown to be due to an increase in the smooth endoplasmic reticulum (Allen and Abrahamson, 1973; Hansell and Ecobichon, 1974; Jonsson et al., 1981; Kimbrough et al., 1972). Lipid-containing vacuoles were also observed in these studies with concentrically arranged membranes surrounding the lipid-containing vacuoles.

the head and muzzle. Another study (Bell, 1983) reported initial lesions consisting of thickening and erythema of the pinna in mice exposed to a 200 ppm Aroclor 1254 diet.

As in the case with acute exposure to PCBs, monkeys exhibit skin lesions when exposed chronically to PCBs. Male rhesus monkeys exposed to 3, 10, 30 or 100 ppm Aroclor 1242 diet for up to 245 days exhibited palpebral swelling and erythema. Similar toxicity was observed in male and female rhesus monkeys fed diets containing 2.5 and 5.0 ppm Aroclor 1248 for 18 months. The females had more severe skin lesions such as alopecia and chloracne (Barsotti et al. 1976).

These same lesions, however, were produced in animals exposed to PCBs devoid of PCDFs. When rhesus monkeys were exposed to 3,3',4,4'-tetra-CB (PCDFs <1 ppm) in the diet, large-scale mortality followed. The skin lesions consisted of squamous metaplasia of sebaceous glands and cystic formation in the eyelids. Nail beds were hyperkeratotic leading to shortening or loss of nails (McNulty et al., 1980). In this same report, other monkeys exposed to 3,3',4,4'-tetra-CB were allowed to recover from PCB exposure for 76 days at which time the animals exhibited normal regeneration of the skin. In a study with cynomolgus monkeys, Hori et al. (1982) found that PCBs devoid of PCDFs did not produce typical skin lesions.

Immune System -- Chronic studies using rhesus monkeys have indicated an apparent effect of PCBs on the immune system. McNulty et al. (1980) found that 3,3',4,4'-tetra-CB produced thymus regression. In another nonhuman primate study utilizing PCB mixtures with or without PCDFs, Hori et al. (1982) found that all compounds tested depressed immunocompetency as alterations in body weights, hematologic, urinalysis and clinical chemistry parameters.

Male Sprague-Dawley rats were fed diets containing 100 ppm Aroclor 1248, 1254 or 1262 for 52 weeks (Allen et al., 1976; Allen and Abrahamson, 1979). Observations continued for 13 weeks following treatment. Appearance, appetite and weight gain were normal in all rats throughout the study. Hematologic parameters and serum protein and albumin/globulin ratio remained normal. Total serum lipids and cholesterol remained elevated throughout the 52-week experimental period and serum cholesterol remained elevated 13 weeks after exposure was terminated. Serum triglycerides from all treatment groups ranged from 20-40% below control levels.

Morgan et al. (1981) reported on the toxicity of feeding diets containing Aroclor 1254 to male and female F344 rats for 2 years. Rats were exposed to levels of 0, 25, 50 or 100 ppm of Aroclor 1254 in the diet. Mortality occurred in 8 and 33, 17 and 21, 42 and 17, and 54 and 29% of the males and females, respectively, in these respective groups. Mean final body weight of all treatment groups were lower than the body weight of the control groups with the exception of the low-dose group males. Beginning at 72 weeks for the high-dose group and 104 weeks for the medium-dose group rats, alopecia, facial edema, exophthalamos, cyanosis and amber colored urine became noticeable.

Long-term studies in nonhuman primates have provided information on a variety of alterations in clinical parameters. Clinical determinations in rhesus monkeys (Barsotti et al., 1976; Allen et al., 1979a; Barsotti, 1981) after 16 months of exposure to 2.5 and 5.0 ppm Aroclor 1248 in the diet

As mentioned previously, minks are sensitive to PCB intoxication. A study (Aulerich and Ringer, 1977) indicated that 2 ppm of Aroclor 1016, 1221, 1242 or 1254 in the diet had no effect on body weight gain, hemoglobin or hematocrit in mink. In another study (Bleavins et al., 1980) Aroclor 1242 and 1016 were fed to male and female pastel mink for ~8 months. Aroclor 1242 was fed at 0, 5, 10, 20 or 40 ppm in the diet and Aroclor 1016 was fed at 0 or 20 ppm in the diet. Aroclor 1242 at levels ≥20 ppm in the diet resulted in 100% mortality. Aroclor 1016 at 20 ppm in the diet resulted in mortality of 25% (3/12) of the females exposed. Necropsy revealed emaciation, an almost complete absence of body fat and gastric ulceration.

Koller and Zinkl (1973) administered 300 ppm Aroclor 1221, 1242 or 1254 by stomach tube, once weekly for 14 weeks, to New Zealand White rabbits. Blood samples were taken every 2 weeks from the five males and five females in each group for determination of blood chemistries. After 2 weeks SGPT and SGOT levels were elevated in Aroclor 1254-treated males. Females developed elevated SGPT and SGOT at 4 and 8 weeks, respectively, after exposure. Aroclor 1221 failed to elevate serum levels of either enzyme throughout the study. Total serum protein, protein fraction levels and BUN did not differ from controls during the study. No hematologic differences were noted between control and treatment individuals. Serum cholesterol was elevated significantly in males treated with Aroclor 1254 as early as 7 weeks.

Developmental and Reproductive Toxicology

Developmental toxicology is the study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in

TABLE V-10

Summary: Teratogenetic, Fetotoxic and Reproductive Effects of Orally Administered PCBs

Species/ Strain	Source of PCBs	Dosage Level and Duration of Treatment	Maternal Response	Progeny Response	Reference
Rabbit	Aroclor 1254	0, 1.0, 10.0, 12.5, 25.0, 50 mg/kg bw/day on days 1-28 of pregnancy; 25 mg/kg bw/day on days 7-28 of pregnancy	Dose ≥25 mg/kg bw: maternal death, weight loss; ≥10.0 mg/kg bw: hepatomegaly; 25 mg/kg bw days 7-28: reduced rate of gain.	≥12.5 mg/kg bw/day: fetal death, resorptions, abortions.	Villeneuve et al., 1971a
Rat/Wistar	Aroclor 1254	0, 6.25, 12.5, 25.0, 50, 100 mg/kg bw/day on days 6-15 of gestation	None reported	None reported	
Rat/Sherman	Aroclor 1254	0, 1, 5, 20, 100, 500 ppm diet from 3-4 weeks of age to termination of 1- or 2-generation study	None reported	F_{1a} 500 ppm: reduced litter size; 100 ppm: reduced litter size; F_{1b} 100 ppm: reduced survival at weaning; 20, 100 ppm: reduced litter size; F_{2a} 100 ppm: reduced litter size and reduced survival at weaning; 20 ppm: reduced litter size; F_{2b} 20, 100 ppm: reduced litter size.	Linder et al., 1974
	Aroclor 1260	0, 5, 20, 100, 500 ppm diet from 3-4 weeks of age to termination of 1- or 2-generation study	None reported	F_{1a} 500 ppm: reduced litter size and reduced survival at weaning. F_{1b} 500 ppm: reduced litter size.	
	Aroclor 1254	0, 10, 50, 100 mg/kg bw/day dosed on days 7-15 of gestation	None reported	F_1 100 mg/kg bw/day: reduced litter size.	
Rat/Sprague-Dawley	Aroclor 1254	0, 25, 50, 100, 200, 300, 600, 900 ppm diet/day on days 6-15 of pregnancy	≥600 ppm: partial anorexia and weight loss.	≥300 ppm: fetal death at delivery. ≥100 ppm: reduced litter weight.	Spencer, 1982
Mice/CD_1	3,3',4,4',5,5'-hexa-CB	0, 0.1, 1.0, 2.0, 4.0, 8, 16 mg/kg bw/day, on days 6-15 of gestation	≥8 mg/kg bw/day: reduced rate of gain, lethargy, vaginal bleeding.	≥4 mg/kg bw/day: fetal mortality, resorptions; ≥2 mg/kg bw/day: increased incidence of cleft palate; ≥4 mg/kg bw/day: increased incidence of hydronephrosis; ≥1 mg/kg bw/day: increased incidence of cream colored liver; ≥1 mg/kg bw/day: increased incidence of undersized renal papillae.	Marks et al., 1981

significantly depressed at the 300 and 600 ppm level. There were no live deliveries at the 900 ppm level.

Baker et al. (1977) administered Aroclor 1254 to Wistar rats through drinking water to study the toxicokinetics of this commercial mixture of PCBs. Drinking water contained 70 ppm Aroclor 1254 emulsified with 0.15% Tween 80. Daily Aroclor 1254 consumption was 6.4 mg/kg bw for 9 weeks. Fetal resorption and increased maternal mortality were reported during this exposure.

An extensive study on reproductive effects of PCBs in rats was performed by Linder et al. (1974). In a 1-generation study, pathogen-free female Sherman rats were fed diets containing either Aroclor 1254 or Aroclor 1260 at levels of 100 or 500 ppm starting at 3-4 weeks of age and terminating exposure after the weaning of the F_{1b} litter. Aroclor 1254 at the 500 ppm level resulted in reduction of the number of litters born, and litter size was reduced. Aroclor 1260 appeared to cause a significant decrease in litter size in F_{1a} rats at the 500 ppm level. F_{1a} survival was also significantly reduced at the 500 ppm level. Aroclor 1260 failed to produce evidence of reproductive toxicity at a level of 100 ppm. Similarly, in the 2-generation study in which pathogen-free male and female Sherman rats were fed diet levels of up to 100 ppm Aroclor 1254 or Aroclor 1260, F_{2a} litters were reduced in size at the 100 ppm level of Aroclor 1254. F_{2b} litters in Aroclor 1254-treated animals were reduced in size at both the 20 and 100 ppm level. These reductions in litter size were significant at the 0.5% confidence level with the exception of the F_{2a} 20 ppm litter, which was significant at the 5.0% confidence level. Ability of animals to wean was reduced by Aroclor 1254 in both studies. Survival at weaning was significantly

Dikshith et al. (1975) examined the effects of Aroclor 1254 on rat testis. Mature male Sprague-Dawley rats were treated by gavage for 7 consecutive days with 50 mg/kg bw Aroclor 1254. At the end of the 7-day treatment period, the rats were allowed a period of recovery. No signs of morbidity were observed. Necropsy examinations were performed on three rats from each group on days 1, 7, 15 and 30 days of recovery. The body weight of rats examined by necropsy at 30 days was significantly reduced compared with controls. Testicular and epididymal size and histological features were normal in treated rats with the exception of a slight increase in testicular interestitial tissue with increased acid phosphatase activity.

One recent study on early postnatally-administered PCBs to male rats was undertaken to determine effects on their subsequent reproductive performance (Sager, 1983). Dams received 8, 32 or 64 mg/kg bw Aroclor 1254 by gavage on days 1-3, 5, 7 and 9 of lactation. At 130 days of age, 3 or 4 males from each treatment group were randomly selected for observation of mating behavior and fertility. PCB treatment at all levels tested interfered with mating behavior and fertility as evidenced by a reduction in numbers of females impregnated. Testicular weights were significantly increased in the 32 and 64 mg/kg groups. Testiculomegaly and subnormal development of accessory sex glands was taken as evidence that PCBs administered in the early postnatal period interfered with circulating levels of androgens.

<u>Mice</u>. A commercial mixture of PCBs, Kanechlor 500, induced formation of cleft palate in mice (Watanabe and Sugahara, 1981). Pregnant ddY strain mice were injected daily on days 6 through 15 of gestation with PCB at 1.0, 2.0, 3.0, 4.0 or 5.0 mg/mouse/day. Maternal mortality was increased in the highest dose group. The incidence of cleft palate in live fetuses was

Marks et al. (1981) clearly demonstrated gross malformations in CD-1 mice resulting from treatment with 3,3',4,4',5,5'-hexa-CB. This isomer was chosen for these studies because it was found to be more toxic and more readily bioaccumulated, and to have a more pronounced toxic effect on liver, thymus and spleen than other isomers tested (Biocca et al., 1981). Pregnant mice were administered 0.1-16 mg/kg bw/day hexa-CB by gavage from day 6 through day 15 of gestation. Although no deaths occurred in exposed dams, lethargy and vaginal bleeding were observed in dams exposed to $\geq$8 mg/kg bw/day. Dams in the 8 and 16 mg/kg bw/day groups suffered a significant reduction in weight gain. Average numbers of live fetuses/dam in the PCB groups demonstrated a significant reduction in a dose-related fashion at doses $\geq$4 mg/kg bw/day. The average number of implants was reduced in the 8 mg/kg bw/day group and fetal resorptions were increased in the 8 and 16 mg/kg bw/day groups. A significant dose-related increase in the incidence of cleft palate occurred in groups dosed at $\geq$2 mg/kg bw/day. An increased incidence of hydronephrosis was also found to be dose-related.

In an effort to demonstrate that PCBs may induce microsomal hydroxylating enzymes that catalyze the breakdown of steroid hormones, Orberg and Kihlstrom (1973) investigated the ability of Clophen A-60 to affect reproduction in mice. NMRI strain sexually mature female mice were fed 0.025 mg/day Clophen A-60 for 72-76 days. Clophen A-60 was found to lengthen the estrus cycle and to reduce the rate of nidation.

Orberg (1977) failed to demonstrate any effect of pre- and postnatally-administered PCBs on the reproductive performance of mice. 2,4',5-Tri-CB or 2,2',4,4',5,5'-hexa-CB was fed at levels of 0.05 mg/day from day 5 of pregnancy to weaning at postpartum day 22 to NMRI strain mice. The males and receiving 10, 25 or 50 mg/kg bw. Dams treated with 25 mg/kg bw on days 7-28 of pregnancy exhibited decreased weight gain and hepatomegaly.

Another study from the same laboratory (Villeneuve et al., 1971b) reported no evidence of developmental toxicity to orally administered Aroclor 1221 or 1254 at levels of 1.0 or 10 mg/kg bw in rabbits. Mature dams were exposed to the Aroclors for the first 28 days of pregnancy. Nidation, fetal growth and development, litter size and placentation were all similar to control rabbits.

<u>Other Species</u>. Mink are especially sensitive to the toxic effects of PCBs. Feeding mink levels of Aroclor 1242 as low as 10 ppm in the diet for 8 months resulted in high mortality, while exposure at 5 ppm caused 25% mortality and reduced fertility of females (Bleavins et al., 1980). By 4 weeks, litters experienced increased mortality and decreased litter biomass. No teratogenicity was observed. Reproductive toxicity was related to feto-toxicity rather than interference with ovulation or nidation because fetal resorptions were found at all stages of gestation. In another experiment, dietary exposure to Aroclor 1016 at 20 ppm produced 25% mortality and reduced reproductive function (Bleavins et al., 1980). Kits nursed by dams fed Aroclor 1016 at 20 ppm had significantly lower body weight at 4 weeks of age. In addition, higher kit mortality between birth and 4 weeks of age was also noted.

Aulerich and Ringer (1977) exposed mink to Aroclor 1254 in the diet at a level of 2 ppm (see Table V-9). They observed a reduction in reproductive function with no apparent maternal toxicity. In another experiment, dietary

1254 at 100 or 400 μg/kg bw/day continuously until a termination of pregnancy. Monkeys dosed at the 100 μg/kg bw/day level delivered term, stillborn infants. The monkey dosed at the 400 μg/kg bw/day level delivered a live infant that subsequently succumbed at 139 days of age to pneumonia. Maternal toxicity was evidenced as fingernail loss and impaired immunocompetence as evaluated by titer developed to tetanus toxoid and sheep erythrocytes.

A longer-term and more intensive study examined the effects of Aroclor 1248 on reproduction in rhesus monkeys (Barsotti et al., 1976; Allen et al., 1979b, 1980). Aroclor 1248 was fed to groups of eight mature female monkeys weighing ~5.6 kg at levels of 2.5 or 5.0 ppm in the diet for ~18 months starting 6 months before breeding to untreated males. On the basis of food intake, the total Aroclor 1248 intake was calculated to be 270±25 and 498±50 mg for the 2.5 and 5.0 ppm diet groups, respectively. Analysis of this batch of Aroclor 1248 revealed ~1.7 ppm PCDFs. This would have provided 4.4 and 8.7 μg PCDFs/kg in the 2.5 and 5.0 ppm Aroclor 1248 diets, respectively. Treated females experienced weight loss and lengthened menstrual cycles accompanied by altered levels of progesterone and estradiol. Conceptions were normal for both groups. Monkeys receiving 2.5 mg/kg delivered five live infants and experienced three early abortions or fetal resorptions, and only one monkey receiving 5.0 mg/kg delivered a live infant. Adult females exhibited signs of toxicity. Live infants had reduced birth weights and, after 2 months of nursing, exhibited facial edema, hyperpigmentation and hair loss and palpebral edema and acneform lesions more severely than their mothers. Within the first year, 3 of these 6 infants had died.

In another study (Allen et al., 1979b), exposure of eight female monkeys to 0.5 or 1.0 ppm of Aroclor 1248 in the diet 3 times weekly for 7 months resulted in total intakes of ~8 or 16 ppm of Aroclor 1248 (see Table V-8). These animals showed no irregularities of menstrual cycle or alterations in serum estradiol or progesterone, and had normal fertility when bred. This exposure produced some fetal loss, infant birth weights were reduced and nursing infants developed focal areas of hyperpigmentation.

Subsequently, 24 adult female monkeys were exposed to diets containing 0.025, 0.25 or 1.0 ppm Aroclor 1016 (Barsotti and van Miller, 1984). After consuming the PCB diets for 6 months, the animals were bred in the 7th month of the experiment. Animals continued consuming PCB diets throughout gestation and 4 months of nursing. The author reported observing no abnormalities of clinical, gross or reproductive parameters. Infants from females exposed to 1.0 ppm diet exhibited significantly ($\leq$0.01) reduced birth weight.

Mutagenicity

Mutagenicity studies of PCBs in Salmonella typhimurium are summarized in Table V-11. PCBs have not shown positive results by themselves, but evidence exists that metabolic activation may result in mutagenic metabolites which may have potential activity with DNA resulting in mutagenic responses (Wyndham and Safe, 1978; Wyndham et al., 1976; Hesse and Wolff, 1977; Hesse et al., 1978; Shimada and Suto, 1978; Stalnicki et al., 1979; Wang et al., 1979; Morales and Mathews, 1979). Evidence also exists that the position of the chlorines on the biphenyl ring influences potential mutagenicity. In addition, it appears that S-9 fractions from different strains may cause different results.

Schoeny et al. (1979) tested Aroclor 1254 for mutagenicity at eight concentrations ranging from 0.5-500 μℓ/plate in strains TA1535, TA1537, TA98 and TA100 of _S. typhimurium_. Aroclor 1254 alone, activated by S-9 hepatic fractions from untreated or Aroclor 1254-induced Sprague-Dawley rats, failed to manifest mutagenicity. Subsequently, this same laboratory, recognizing the heterogeneous nature of commercial Aroclor, conducted a study of the mutagenicity of four separate PCB congeners (Schoeny, 1982). Using materials of 99% purity, eight doses of 4-chlorobiphenyl and five doses each of 3,4,3',4'-tetra-CB; 2,4,2',4'-tetra-CB and 2,4,6,2',4',6'-hexa-CB were tested for mutagenicity in _S. typhimurium_ (see Table V-11). Mutagenicity was not demonstrated with any of these PCBs with or without the addition of hepatic S-9 fractions. In this same study, the author likewise failed to demonstrate mutagenicity of dibenzofuran or various polychlorinated dibenzofurans, often considered common contaminants of PCBs.

Wyndham et al. (1976) have attempted to relate degree of mutagenicity to degree of chlorine substitutions on the biphenyl moiety. Using levels of 10, 50, 100 or 200 μg/plate of the 4-mono-CB, Aroclor 1221 [average chlorine content 1.15 (2 Cl/molecule)], 2,2',5,5'-tetra-CB (4 Cl/molecule) or Aroclor 1254 (average 4.96 Cl/molecule), these authors demonstrated a pronounced mutagenicity (>2000 mutant colonies/plate) of 4-mono-CB compared with the more highly chlorinated PCBs.

Heddle and Bruce (1977) examined the mutagenicity of Aroclor 1254 in a group of 61 potential mutagens and compared mutagenicity with the production of cytogenetic effects in mice. Aroclor 1254 was found to be nonmutagenic in the _S. typhimurium_ bioassay and negative in both cytogenetic evaluations.

These authors concluded that the products tested did not indicate clastogenic effects, but pointed out that these products differed from commercially available PCB products in that the impurities ordinarily present in commercial products were not present here.

A cytogenetic study of Aroclor in rats was performed by Green et al. (1975a). Aroclor 1242 was given orally in single doses of 1250, 2500 or 5000 mg/kg bw or at multiple doses of 500 mg/kg/day for 4 days to groups of eight male, random-bred Osborne-Mendel rats. Aroclor 1254 was orally administered at 75, 150 or 300 mg/kg/days for 5 consecutive days to groups of eight rats. The animals were sacrificed 24 hours after the last dose was given. Aroclor 1242, the more toxic product, did not produce cytogenetic damage in spermatogonia or in cells from the bone marrow. Aroclor 1254 did not show any evidence of cytogenetic damage in the bone marrow cells. The effects of this product on spermatogonia were not evaluated. The number of bone marrow cells observed in mitosis appeared to be depressed ($p<0.05$) in the Aroclor 1254 groups at the mid (150 mg/kg/day) and high (300 mg/kg/day) treatment levels. Mitosis in bone marrow cells of Aroclor 1242-treated groups did not appear to be depressed, but spermatogonial mitosis did appear to be reduced in the 500 mg/kg/day for 4 days ($p<0.01$) and the 5000 mg/kg ($p<0.05$) groups. A later cytogenetic study of bone marrow and spermatogonia in male Holtzman rats (Garthoff et al., 1977) confirmed the negative findings of the previously cited study.

Likewise, Dikshith et al. (1975), in a more comprehensive study of the effects of orally administered Aroclor 1254 on rat testis, found no significant evidence of chromosomal aberration caused by PCBs. Aroclor 1254 was

Carcinogenesis

PCBs have been tested for carcinogenicity in rats and in mice by incorporation of particular commercial PCB preparations into the diet. Eight separate PCB feeding studies and one study of topical application to the skin are considered. Studies in which the PCB preparations were administered in conjunction with other agents are also discussed in this section.

Carcinogenicity. The feeding studies demonstrate the carcinogenicity of some commercial PCB preparations although it is not known which of the PCB congeners in such preparations, or which of their metabolites, are responsible for the carcinogenicity demonstrated by the tests. The liver appears to be the primary target organ that exhibits a tumorigenic and carcinogenic response to PCB exposure. The studies reviewed had, in varying degrees, shortcomings that modify the meaning of the results and the contribution the study made to the overall assessment of PCB carcinogenicity.

Rat Studies -- PCBs have produced a variety of oncogenic effects in the rat liver. Historically, adenofibrosis was the first hepatic lesion to be described in animals chronically exposed to PCB mixtures (Kimbrough et al., 1972; Kimura and Baba, 1973). Kimura and Baba (1973) studied Kanechlor 400 incorporated into the test diet of male and female Donryu rats fed diets initially at 38.5 ppm and increased periodically to an upper limit of 616 ppm to keep pace with body weight gain. The upper level resulted in severe body weight loss and was accordingly reduced to 462 ppm for the remainder of the trial. The duration of the study ranged from 159-538 days for the different animals, but there were two intervals of 4 weeks each during which

TABLE V-12

Change in Rat Body Weight Following Chronic Exposure to Kanechlor 400*

PCB in Diet (ppm)	No. Animals	Initial Weight (g)	Final Weight (g)	Percent Difference
		MALES		
450	1	199	309	+55
900	1	192	273	+42
>1200	8	210	259	+23
Control	5	205	462	+125
		FEMALES		
700	1	158	137	-13
1100	3	160	162	0
>1200	6	196	196	0
Control	5	196	323	+65

*Source: Kimura and Baba, 1973

TABLE V-13

Change in Rat Body Weight Following Chronic Exposure to Several Kanechlor Formulations*

Product	ppm	Initial Weight Gain Average	Percent Increased Average	No. Animals
		52-Week Exposure Cases		
K-500	1000	126	129	13
	500	123	207	16
	100	124	300	25
K-300	1000	128	228	15
	500	135	239	19
	100	125	304	22
Control	0	130	325	18
		40-Week Exposure Cases		
K-400	1000	163	23	10
	100	175	129	16
Control	0	NA	NA	NA
		28-Week Exposure Cases		
K-400	500	188	53	8
Control	0	NA	NA	NA

*Source: Ito et al., 1974

NA = Not applicable

Although only a single dose was selected and only female animals employed, the study demonstrates hepatocarcinogenicity of Aroclor 1260 in female Sherman rats. Kimbrough et al. (1972), using 10 animals of each sex given each of three doses (100, 500 and 1000 ppm) of Aroclors 1260 and 1254, did not produce either neoplastic nodules or hepatocellular carcinoma in this same strain of rat when the study ran less than a year. In this preliminary study Aroclor 1254 produced adenofibrosis in 10/10 male rats. This finding suggests that hepatocellular carcinoma results when the dose is low enough to permit the study to be run for a sufficient length of time without interfering toxicity. The 14% incidence of hepatocellular carcinomas in the large experiment also explains why it would be unlikely to have detected this cancer in experiments run on a small number of animals: 14% of 24 animals would be 3-4 animals and hepatocellular carcinoma would only have appeared after about a year. Experiments that reduced the number below 24 before the earliest time to tumor would not be expected to yield a detectable carcinoma incidence.

Even though this experiment is probably an adequate animal study to use for risk assessment, it also has a problem in that a mixture of compounds was tumorigenic. The active ingredient(s) in the mixture is most likely limited to a few of the molecular species. A tumor yield of 14%, which is due to the presence of a molecular species that constitutes only a fraction of the composition of the administered material, would be considered potent.

The carcinogenicity of PCBs was investigated in a study sponsored by NCI (1978). Groups of 24 F344 rats of each sex were fed diets containing

TABLE V-14

Proliferative Lesions of the Liver in Fischer Rats Fed Aroclor 1254*

	Males		Females	
	Hepatocellular Carcinomas	Hyperplastic Nodules	Hepatocellular Carcinomas	Hyperplastic Nodules
Controls	0	0	0	0
25 ppm	0	5/24	0	6/24
50 ppm	1/24	8/24	1/24	9/22
100 ppm	3/24	12/24	2/24	17/24

*Source: NCI, 1978

A recent paper reevaluating this same study (Ward, 1985), cites a dose-related depression of body weight gain for both sexes and a decrease in survival for male rats. Increased incidence of gastric intestinal metaplasia and adenocarcinoma was confirmed. Hepatocellular adenomas, carcinomas and eosinophilic and vacuolated hepatocellular foci were usually found in dosed rats only and in these animals their numbers were significantly increased. The conclusion of the author was that the appearance of the potentially preneoplastic lesions and tumors in the liver and stomach of the PCB-treated rats did not occur spontaneously.

The hepatocarcinogenic effect of dietary administration of 100 ppm Clophen A-30 or A-60 (Authors stated that Clophen A-30 and A-60 did not contain chlorinated dibenzofurans) for 832 days was tested in male weanling rats (Schaeffer et al., 1984). Twenty-one percent of the Clophen A-60 treated animals that died in the first 800 days experienced hepatocellular carcinoma, while only 2% of the animals died with similar lesions in the Clophen A-60. Preneoplastic lesions were first observed after day 500 followed by tumors after 700 days on the PCB diets. An increase in neoplastic nodules and hepatocellular carcinomas was observed to increase with time. Statistically significant increases of hepatocellular carcinomas were observed in male rats fed Clophen A-60. However, rat fed with Clophen A-30, had a statistically significant increases of neoplastic nodules or/and hepatocellular carcinomas together. Interestingly, the total mortality rate and the incidence of thymoma and inflammation of the genital/urinary tract in the experimental animals was reduced when compared with the controls. This protective effect has been seen in other halogenated aromatic hydrocarbons (Kociba et al., 1979).

TABLE V-15

Progression of Preneoplastic and Neoplastic Hepatocellular Lesions in Male and Female Sprague-Dawley Rats Exposed to Aroclor 1260[a,b]

Lesion	Number of Livers with Lesions of Each Three Sampled															
	1 Month		3 Months		6 Months		9 Months		12 Months		15 Months		18 Months		24 Months	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Focus	0	0	2	2	3	3	3	3	3	3	3	3	3	3	3	3
Area	0	0	0	0	1	0	2	1	0	3	1	3	0	3	3	2
Neoplastic nodule	0	0	0	0	0	0	0	0	0	1	0	3	0	3	1	3
Trabecular carcinoma	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	2
Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2

[a]Source: Norback and Weltman, 1985

[b]These lesions were not present in sequentially sampled control liver.

TABLE V-16

Incidence of Hepatocellular Neoplasms in Male and Female Sprague-Dawley Rats Exposed to Aroclor 1260[a]

	% Incidence in Treated Animals[b]		% Incidence in Control Animals[b]	
Number of Animals	M	F	M	F
	46[c]	47[d]	32[c]	49[e]
Trabecular carcinoma[f]	4 (2)	40 (19)	0	0
Adenocarcinoma[f,g]	0	51 (24)	0	0
Neoplastic nodule only	11 (5)	4 (2)	0	2 (1)
Negative	85 (39)	4 (2)	100	98 (48)

[a]Source: Norback and Weltman, 1985

[b]Figures in parentheses denote number of animals that survived ≥18 months.

[c]Includes 8 animals that had received a partial hepatectomy during the first 18 months.

[d]Includes 7 animals that had received a partial hepatectomy during the first 18 months.

[e]Includes 10 animals that had received a partial hepatectomy during the first 18 months.

[f]Animals containing neoplastic nodules plus carcinoma were only included in the carcinoma category.

[g]Animals with trabecular carcinoma and adenocarcinoma were only placed in adenocarcinoma category.

animal housing conditions and were not due to toxicity. At the end of 11 months the surviving animals were sacrificed. Only those animals that showed gross abnormalities were examined microscopically.

The livers of animals treated with the Aroclor congeners were enlarged. Control animals had liver weights that were, on the average, 6% of their body weight. Treated animals had livers that were 7.5% of their body weight for the group exposed for 6 months and 25.5% of their body weight for those exposed for 11 months. Livers of treated animals showed multiple abnormalities including abnormal porphyrin metabolism as indicated by UV fluorescence. Adenofibrosis, a possible premalignant lesion, was also found among treated mice.

At the end of 11 months the surviving animals were sacrificed and the incidence of tumors of the liver was noted: 0/34 and 0/24 for the two control groups and 9/22 (40.1%) (10 hepatomas in 9 animals) in the 11-month exposure group; 1/24 (4%) of the animals in the 6-month exposure group had hepatomas. It should be noted that the BALB/CJ mouse has a low spontaneous incidence of hepatoma strain.

The experiment provides positive evidence that Aroclor 1254 is capable of producing a 40% incidence of hepatoma in male BALB/CJ mice at a dosage level of 50 mg/kg/day given for 11 months. The study provides confirmatory evidence of the carcinogenicity of commercial PCB mixtures in mice. In this case 300 ppm Aroclor 1254 produced a 40% incidence of hepatoma in male BALB/CJ mice in 44 weeks, and in the Ito et al. (1973) study Kanechlor 500 at 500 ppm in the diet for 32 weeks produced a 40% incidence of hepatocellular carcinoma in male dd mice.

TABLE V-17

Effects on Liver Tumorigenesis and Carcinogenesis: Feeding Studies Using Various Commercial PCB Preparations

Species/ Strain/Sex	Agent	Duration	Exposure (ppm)	No. Animals	Results and Comment	Reference
Rats/Sherman (F)	Aroclor 1260	90 weeks	100	200/group	Hepatocellular carcinoma 14% (26/184) compared with 0.58% (1/173) controls, 78% neoplastic nodules compared with 0 in controls, no other treatment-related toxicity, study well done but limited to single dose and to females: shows carcinogenicity in female rats of Aroclor 1260.	Kimbrough et al., 1975
Rats/Sprague-Dawley (M&F)	Aroclor 1260	29 months	100 for 16 months, 50 for 8 months, none for 5 months	70/group	95% hepatocellular tumors in female rats 45/47, 15% in male rats 7/46	Norback and Weltman, 1985
Rats/Fischer 344 (M&F)	Aroclor 1254	104-105 weeks	100 50	24/group	In males at 100 ppm, 8-10% hepatocellular carcinoma. Not statistically significant but study design would have required 35% or greater incidence for statistically significance. Results consistent with Kimbrough et al. (1975) and supports effect in males.	NCI, 1978
Rats/Donryu (M&F)	Kanechlor 400	22-77 weeks	38-462	10/group	Excessive toxicity, MTD exceeded, adenomatous nodules in females with total dose of 1200 mg or more; test too short, too few animals at risk, excessive toxicity. Test inadequate.	Kimura and Baba, 1973
Rats/Wistar (M)	Kanechlors 500 400 300	28-52 weeks	 1000 500 100	22-25?/group	Nodular hyperplasia with Kanechlor 500 and Kanechlor 300, not statistically significant, duration of study too short, excessive toxicity. Test inadequate.	Ito et al., 1974
Mice/dd (M)	Kanechlors 500 400 300	32 weeks	 500 250 100	12/group	Hepatocellular carcinoma with Kanechlor 500 at 500 ppm 41.7% (5/12) and liver nodules in 58.3% (7/12), demonstrates carcinogenicity in male mice.	Ito et al., 1973

lesions. In addition, adenocarcinomas were observed in stomach, jejunum or cecum in treated animals. Morgan et al. (1981), in a later review of tissue specimen (NCI, 1978) detected, three additional adenocarcinomas of the stomach at sites of alkaline phosphatase (AP) positive. The NCI (1978) and Morgan et al. (1981) results are especially important in light of the fact that the sample sizes used by NCI were unusually small.

Saeffer et al. (1984) tested Clohen A-30 and Clophen A-60 in Wistar male rats by long-term feeding over a period of 118-119 weeks. Clophen A-60 induced a statiscally significantly increased incidences of hepatocellular carcinomas in rats. However, Clophen A-30 induced statistically significant increased incidence of neoplastic nodules, carcinomas alone were not significant.

In a more recent study of Norback and Weltman (1985) where 70 male and 70 female Sprague-Dawley rats were fed a diet containing polychlorinate biphenyl mixture (Aroclor 1260, 100 ppm for 16 months and 50 ppm for an additional 8 months) for 2 years followed by a control diet for 5 months, Aroclor 1260 induced highly statistically significant increases of liver tumors in female rats (45/47 treated vs. control 1/48). In males, liver tumor incidences were statistically significant but less striking (7/46 treated vs. control 0/32). These results strongly support earlier hepatocellular tumor evidence in Sherman rats fed Aroclor 1260 in the Kimbrough et al. (1975) study. Polychlorinated biphenyl Aroclor 1260 induced significant hepatocellular carcinogenic effects in two rat studies (Kimbrough et al., 1975; Norback and Weltman, 1985). Kanechlor 500 induced statistically significant incidences of liver tumors in dd mice fed 550 ppm for 32 weeks.

The question arises as to how to use these studies for risk assessment. It is difficult if not in fact impossible at present to scientifically to assess the toxic nature of the mixtures of the majority of the commercial preparations. The biological significance of this heterogeneity is that each of the isomers has its own particular toxicokinetic, metabolic and enzyme induction profile that is as much a function of the position of its chlorine substituents and the total number of chlorine substituents it contains. The extent to which any particular isomer contributes to or antagonizes the carcinogenic process is not known. The resultant carcinogenicity observed when the mixture is administered may-be the work of one individual isomer, present in a small quantity, or of another isomer present to a larger extent, e.g., 25% of the composition of the mixture.

Other Related Studies

Promotional and Antipromotional Studies. Long-term exposure to mixed commercial PCBs has been associated with the development of hepatocarcinogenic effects in mice and rats. There is little evidence to suggest that pure PCBs are mutagenic or otherwise genotoxic. The role of PCB-induced liver microsomes as potent activators of many chemicals to mutagenic derivatives has been established. Recent evidence indicates that PCBs may also be protective against other carcinogenic events.

Promotion -- Ito et al. (1973) evaluated Kanechlor 500 in combination with BHC (Table V-18). These data show that when male dd mice were given Kanechlor 500 (250 ppm) in their diet for 32 weeks with or without one of the BHC compounds, they responded by yielding a higher incidence of hepatocellular carcinoma than when either the BHC or the Kanechlor was given alone.

In a brief communication of a short-term study, Ito et al. (1978) demonstrated the ability of PCB (mixture not stated or characterized) and other organic compounds to enhance nodular liver hyperplasia induced by feeding 2-FAA, a known liver cancer inducer, to rats. Male Fischer rats weighing 155 g were used. Two groups of control rats were fed diets containing 200 ppm 2-FAA for the 10-week trial; one group was partially hepatectomized in the third week of the study. There were two PCB treatment groups, both fed a diet containing 1000 ppm PCB for the entire 10-week experimental period, and one group partially hepatectomized in the third week of the study. PCB-fed rats had livers containing significantly ($p<0.05$) more hyperplastic nodules/10 cm^2 than control rats. Partial hepatectomy significantly ($p<0.001$) increased the incidence of nodular hyperplasia in the treatment groups.

The data show that while each agent alone produced some reduction in growth compared with controls, the combined effects were substantial. It is not possible to tell from this experiment whether the effects observed on tumor growth were due to a general systemic debilitation or whether the effects represent specific drug-related responses. The overall toxicity of the combined agents was not adjusted so that it would be no greater than the level of toxicity of each alone.

A report published by DiGiovanni et al. (1978) in which 100 μg of Aroclor 1254 was applied to the skin of CD-1 mice followed by repeated applications of the phorbol ester promoter, DMBA, stated that the data showed weak initiator activity with only 0.2 papillomas per mouse. The tumor-promoting activity of Aroclor 1254 was investigated in a study by Berry et al. (1978). Groups of 30 female CD-1 mice were used. The animals

TABLE V-19

Percent Weight Change in Kanechlor 500 Exposed Rats*

Weight Change %		Weight Change %		Weight Change %	
Control	+180	Control	+180	Control	+180
3-MeDAB	+150	PCB + 3-MeDAB	+107	PCB + 3-MeDAB + DEN	+65
DEN	+137	PCB + DEN	+73	PCB + 2-FAA + DEN	+52
2-FAA	+116	PCB + 2-FAA	+100		
PCB	+112				

*Source: Adapted from Makiura et al., 1974

MeDAB = 3'-methyl-4-dimethyl-aminoazobenzene; DEN = Diethylnitrosamine; 2-FAA = N-2-fluorenylacetamide

TABLE V-20

The Liver and Body Weight Ratio and the Number of Liver Tumors Produced in Offspring Rats Exposed to PCB through Their Dams and Treated with DEN after Weaning[a,b]

Group No.	Treatment		Sex of Offspring	Liver Weight as Percent Body Weight		Average Number of Liver Tumors (>5 mm)/Rat	
	Dam	Offspring		20 week	24 week	20 week	24 week
1	PCB 200/mg/kg 3 times	DEN 50 ppm 5 weeks	male	5.3 ± 0.1	6.4 ± 0.3	1.0 ± p04[c] (6,4,6)	2.0 ± 0.7[c] (14,5,7)
			female	5.1 ± 0.3	6.2 ± 0.2	0[c] (0,0,8)	0.4 ± 0.3 (3,2,8)
2	PCB 40/mg/kg 3 times	DEN 50 ppm 5 weeks	male	5.3 ± 0.2	6.3 ± 0.5	1.3 ± 0.4[c] (10,6,8)	2.8 ± 0.7 (17,6,6)
			female	5.5 ± 0.1	5.8 ± 0.2	0.6 ± 0.3 (5,4,8)	0.7 ± 0.4 (5,3,7)
3	None	DEN 50 ppm 5 weeks	male	6.0 ± 0.4	7.5 ± 0.6	3.0 ± 0.7 (21,6,7)	4.6 ± 0.7 (37,8,8)
			female	5.6 ± 0.3	6.1 ± 0.4	1.1 ± 0.4 (9,5,8)	1.4 ± 0.5 (10,4,7)

[a]Source: Nishizumi, 1980

[b]The data are expressed as means ± SE. Numbers in parentheses are the total number of liver tumors/group, the number of rats bearing liver tumors, and the number of rats sacrificed, in that order.

[c]Significant at the 5% level as compared with group 3.

considered a positive control. In this trial using small numbers and a short experimental period, the authors found that PCB fed at these levels did not effectively enhance 3-MC-induced cervical carcinoma.

Considerations in Evaluating the Carcinogenic or Anticarcinogenic Potency of the PCB Preparations Tested. The manufacturing process for commercial PCB products, such as the Aroclors, yields products composed of a mixture of 20-60 different polychlorinated biphenyl molecules. Individual lots of Aroclors of the same average chlorine content differ greatly in both their components and amounts of each component. The extent to this variable composition can be seen from the analyses of three different Aroclor 1260 preparations carried out in different laboratories. One preparation contained 26 PCBs, another 48 different PCBs and the third was only partially analyzed. The number of isomers found in the preparations for each level of chlorination is shown in Table V-21.

In addition to the variability in polychlorinated biphenyls in the commercial PCB preparations, there are also a number of impurities in the products. Among the impurities are PCDFs, which are highly toxic and are under test for carcinogenicity.

Several points concerning the interpretation of carcinogenicity data, and risk assessments based on the data, hinge upon the recognition of the qualitative and quantitative variability among commercial preparations.

1. Data on purified isomers show that the toxic, metabolic and pharmacokinetic behavior of the different component molecules varies not only with the degree of chlorination, but also with the position of the chlorine atoms.

2. Metabolism of purified isomers has been extensively studied. The hydroxylated metabolites of some 18 different individual PCBs were analyzed. It appears that predictable patterns of hydroxylation occur that indicate that the major pathway for most of the molecules involves direct hydroxylation. At least three different molecules among those studied produced products that indicated utilization of an alternate pathway. These three compounds were 4,4'-di-CB, 2,2',5,5'-tetra-CB and 2,2',4,4',5,5'-hexa-CB. The alternate pathway for these three compounds involves the formation of arene oxide intermediates. Such intermediates would be expected to be carcinogens and mutagens based on studies on well known carcinogens. If the carcinogenicity of the commercial preparations was due solely to these components the potency of the preparations could be calculated on the amount of these isomers present, the percentage of parent compound that utilized this alternate pathway and the pharmacokinetics of the intermediates formed. Table V-22 shows the results of analyses of three different Aroclor 1260, and three different Aroclor 1254 preparations for the presence of these arene oxide-forming compounds.

   Since only a small fraction of the parent compound utilizes the arene oxide pathway, it is highly unlikely that the carcinogenic potential of PCB mixtures is due entirely to this genotoxic reaction. Indeed, the genotoxicity of the products and even these specific isomers is in doubt as judged by short-term mutagenicity tests. If the carcinogenicity observed with the Aroclors is due to the initiating activity of epoxides that may be formed as metabolic intermediates, then the activity in the preparations is too low to be detected _in vitro_, or requires other _in vivo_ conditions to be expressed.

   The metabolic data, along with the information on chemical analyses, and the _in vitro_ tests all suggest that if these components do act as initiators their role in the carcinogenicity may be contributory but is unlikely to be the sole mechanism involved. Recent findings indicate that short-term exposures to 2,2',4,4',5,5'-hexa-CB, 2,2',4,4'-tetra-CB and Aroclor 1254 during liver cell proliferation do not show initiating action in an _in vivo_ assay that detects both hepatic and nonhepatic initiating carcinogens (Hayes et al., 1985). It is, therefore, unsatisfactory to calculate the potency on the basis of exposure to "possible" active components, or to calculate the potency on the basis of exposure to any of the other components, some of which are scarcely metabolized at all.

3. One of the most striking findings concerning the variability of the components of the commercial products is the differing enzyme inducing capacities of particular isomers even at the same level of chlorination. The enzymes induced range from those that are involved in metabolism of PCBs themselves to others that have been implicated as activators and inactivators of other procarcinogens or carcinogens, respectively (Cytochrome P-450 and P-448 associated monooxygenase systems).

The mixed nature of the PCBs would be reflected in mixed enzyme induction, some of which will be capable of reducing the carcinogenic effect and some of which will increase the carcinogenic effects.

4. These examples show why the test data on the carcinogenicity of PCBs generated by use of commercial preparations such as the Aroclors and Kanechlors can provide only a net effect picture of the many and varied effects of the individual components in the preparations. The carcinogenicity that is manifested reflects the sum of vectors that represent partial additive, synergistic and antagonistic effects of numerous individual components. Potency and exposure are basic parameters used in risk estimation.

5. It can be said, however, that it is very likely that the potency of any commercial PCB preparation may be considerably higher or lower than any figure obtained by utilizing the dietary level of exposure as a basis for calculation.

The identification of specific PCB structures in human tissues may be important not only for assessment of long-term persistence but also for evaluation of potential health effects. The importance of the latter is due to the specificity of toxicity and inducibility of mixed function oxidase enzymes by these persistent PCB isomers and congeners. At the present time, the consequence of the persistence and bioaccumulation of these specific PCB congeners and isomers is unknown.

Acute and Short-Term Exposure

Unlike animal studies (Chapter V), there is little information regarding acute or short-term PCB exposure conditions nor any reports of possible consequences of the exposure in humans. The majority of the data on PCBs and humans comes from long-term exposure incidents, that is, occupational exposure or undetermined exposure duration such as occurred with direct introduction of PCB-containing material into the food chain from contaminated rice oil.

Chronic Exposure

Because of the chemical complexities of PCBs and the nature of PCB exposure in humans, it is not surprising that data on the behavior of specific PCB isomers and congeners as well as on effects of contaminants alone or in combination on the human system do not exist.

The problems associated with considering PCBs as one entity is presented in the literature on human health effects of PCBs. As previously pointed out, individual PCB isomers and congeners as well as the contaminants of PCB

Skin -- The most commonly encountered dermatologic symptom associated with PCB exposure is chloracne. Chloracne is produced upon exposure to chlorinated hydrocarbons, for example, napthalenes and biphenyls. The skin lesion manifests itself as follicular keratosis with comedo formation and acneform eruptions. At first the lesion was thought to be a contact phenomenon as it developed on skin not covered by clothing, but subsequently it has been determined that systemic exposure to PCBs will also produce the dermatitis.

Differences in the lesions occur with the amount of chemical exposure, patient age and lesion site. Although there is one report that correlated time of exposure with severity of lesions (Schwartz, 1943), other reports indicate that there is no good correlation of occurrence of chloracne and its severity with duration of employment (Fischbein et al., 1979; Ouw et al., 1976). Thus, it appears that individual susceptibility to chloracne is more important than duration and extent of PCB exposure.

Many case studies in the literature describe varying degrees of chloracne as a result of occupational exposure to PCBs. Early case studies of occupational PCB exposure were reported by Jones and Alden (1936), Drinker et al. (1937), Schwartz (1943) and Meigs et al. (1954). Jones and Alden (1936) reported 16 cases of chloracne among workers employed in the manufacture of PCBs; these are summarized in Table VI-1. These workers were also exposed to impure benzene.

PCB air concentrations have been reported and related to the occurrence of chloracne. The air concentration of 0.1 mg Aroclor/m^3 was associated

TABLE VI-1 (cont.)

Case Number	Age (years)	Race	Duration of Exposure (months)	Type of Skin	Type of Eruption
12	20	white	2	seborrheic	few comedones; occasional abscesses
13	37	white	NR	average	occasional comedones
14	23	Negro	12	average	very few comedones
15	22	white	NR	seborrheic	scattered comedones
16	20	Negro	NR	seborrheic	diffuse comedones; few cysts on back and face

*Source: Jones and Alden, 1936

NR = Not reported

TABLE VI-2

Duration of PCB Exposure of 326 Capacitor Manufacturing Workers*

Duration (years)	Number of Workers	Percent
<5	33	10.1
5.0-9.9	68	20.9
10.0-14.9	57	17.5
15.0-19.9	37	11.4
20.0-24.9	95	29.1
≥25.0	36	11.0

*Source: Fischbein et al., 1979

TABLE VI-4

Prevalence of Reported Dermatologic Symptoms Among 326 Capacitor Manufacturing Workers*

Symptom	Number	Percent
Rash	128	39.3
Burning sensation	81	24.8
Acne	35	10.7
Pigmentation (darkening)	8	2.5
Thickening	12	3.7
Discoloration of fingernails	8	2.5

*Source: Fischbein et al., 1979

TABLE VI-5

Clinical Features of Six Electrical Workers with Chloracne*

			Skin Lesions		
Case No.	Age (years)	Age at First PCB Exposure	Age at Onset	Current Findings	Affected Regions
1	49	27	39	vermicular scars, comedones, superficial cysts and suppurative folliculitis	abdomen, thighs
2	26	16	22	vermicular scars, comedones, superficial cysts, and suppurative folliculitis	face, neck
3	50	20	23	vermicular scars, comedones, superficial cysts, and supperative folliculitis	neck, shoulders arms, back
4	43	28	40	vermicular scars	arms, back, legs
5	38	24	37	folliculitis (possibly chloracne)	scrotum
6	49	42	45	comedones with erythema (possibly chloracne)	neck, sternum

*Source: Maroni et al., 1981a,b

Direct Introduction of PCBs into Foodstuffs

Yusho Incident. The first documentation of human effects as a result of ingestion of PCBs was derived from the Japanese poisoning incident that occurred in 1968. In 1968, the victims suffered an acute toxicosis from consuming rice oil contaminated with an industrial oil (a commercial brand of PCBs), Kanechlor-400 consisting of a mixture of polychlorinated biphenyls (PCB), polychlorinated dibenzofurans (PCDF) and polychlorinated quinones (PCQ). The average total amount of PCBs consumed was estimated to be ~2 g, with ~0.5 g being the least total amount consumed by an affected group of some 325 people at the time (Kuratsune et al., 1972). The PCB oil that got into the rice oil was estimated to contain 5000 ppm PCDFs, some 250 times more concentrated than the 18 ppm found in Kanechlor 500 by GC/MS methods (Nagayama et al., 1976). The presence of the potent toxicant PCDFs in the Yusho oil probably contributed to the overall toxicologic effects seen in Yusho patients.

Yu-Cheng Incident. A similar mass outbreak of a peculiar skin disease was recorded in Taichung and Changhwa in Central Taiwan. The cause of the disease was later identified to be the ingestion of rice bran oil contaminated with PCBs, and there were >1900 victims. Blood PCB levels of 66 affected persons ranged from 11-720 ppb (mean 49 ppb) at ~9-12 months after consumption of the PCB-contaminated oil (Chen et al., 1980).

The presence of polychlorinated quaterphenyls and dibenzofurans was documented (Chen et al., 1981). The PCDF levels in the Taiwan episode were less than that in Japan. The rice oil consumed in Taiwan consisted of larger percentages of penta-, hexa- and heptachlorobiphenyls than did that

Hites, 1983). Rappe et al. (1979) also reported similar observation in a Yusho patient.

A correlation between the severity of clinical symptomatology in Yusho patients and the estimated contaminated oil ingestion (PCBs+PCFDs+PCQs) was reported (Kuratsune et al., 1972; Nagayama et al., 1976; Hayabuchi et al., 1979). However there is much evidence to support the hypothesis that PCDFs and not PCBs are responsible for the disease. Analysis of the concentrations of PCDF and PCB in the liver and adipose tissue of Yusho patients and of control subjects killed in traffic accidents revealed comparable PCB concentrations in tissues of the two groups, but PCDF (in the range of ppb) only in the organs of Yusho patients (Masuda and Kuroki, 1982). Other evidence of the importatnce of PCDF and PCB in determining the Yusho and Yu-Cheng syndrome has been obtained more recently. Kashimoto et al. (1985) compared the blood levels of Yusho (11 years after the outbreak) and Yu-Cheng patients with that of occupationally PCB exposed workers (19 years after termination) and unexposed people. In spite of high levels of PCBs in all the samples, detectavle amounts of PCDFs were only found in the blood of Yu-Cheng patients. In 113 Yu-Cheng patients there was a clear correlation between the blood PCDF concentration and the severity of dermatological symptoms. PCQs were present in the blood of all the Yu-Cheng patients 6 months after exposure and in 54 of the 56 living Yusho patients 11 years after the outbreak. The presence of PCQs in blood can be considered a good marker of past ingestion of contaminated oil.

In the blood of Yu-Cheng patients there was a sidtinctive PCB pattern, very different from the original pattern (Masuda et al., 1985) and richer in the more chlorinated isomers (for example, 2,3,4,5,3',4'-hexa-CB is a PCB

__Immune System__. PCB exposure in the human has been shown to affect the immune system. Shigematsu et al. (1978) reported that human subjects who consumed PCB contaminated rice oil were more susceptible to respiratory tract infections. Yu-Cheng patients had lower serum IgA and IgM, decreased percentages of T cell subpopulations (Lii, Y-C and Wu, Y-C, 1985, Chang et al., 1980a,b) and decreased delayed type skin hypersensitivity response to streptokinase and streptodornase (Chang et al., 1980a,b, 1981).

__Reproductive System__. The maternal-perinatal system also appeared to be affected with the consumption of PCB-contaminated rice oil. From these incidents it is apparent that PCBs cross the placenta and can be transmitted in mothers milk (Abe et al., 1975; Yoshimura, 1974; Kodama and Ota, 1980; Kuratsune, 1976).

Embryos, fetuses and neonates (2-3 months old) are a subpopulation at special risk because of inherent physiological differences from the adult human. This subpopulation usually lacks the hepatic microsomal enzyme systems, including the glucuronidation pathway, that are capable of oxidizing PCBs to facilitate the detoxification and excretion of these compounds (Calabrese and Sorenson, 1977; Gillette, 1967; Nyhan, 1961). Breast-fed infants are at greater risk also because of a steroid excreted in human breast milk, but not in cow's milk, that inhibits glucuronyl transferase activity, and thus glucuronidation and excretion of toxicants such as PCBs, by >20% (Calabrese and Sorenson, 1977; Gartner and Arias, 1966).

Yamashita (1977) reported four cases of infants born to mothers who had Yusho during pregnancy. The amount of PCB-contaminated oil consumed during pregnancy was ~1.1-10.5 ℓ. Maternal symptoms included acneform eruptions,

TABLE VI-7

Percent Distribution of Signs and Symptoms of Yusho Among 189 Persons*

Symptoms	Males (n=89)	Females (n=100)
Dark brown pigmentation of nails	83.1	75.0
Distinctive hair follicles	64.0	56.0
Increased sweating at palms	50.6	55.0
Acnelike skin eruptions	87.6	82.0
Red plaques on limbs	20.2	16.0
Itching	42.7	52.0
Pigmentation of skin	75.3	72.0
Swelling of limbs	20.2	41.0
Stiffened soles in feet and palms of hands	24.7	29.0
Pigmented mucous membrane	56.2	47.0
Increased eye discharge	88.8	83.0
Hyperemia of conjunctiva	70.8	71.0
Transient visual disturbance	56.2	55.0
Jaundice	11.2	11.0
Swelling of upper eyelids	71.9	74.0
Feeling of weakness	58.4	52.0
Numbness in limbs	32.6	39.0
Fever	16.9	19.0
Hearing difficulties	18.0	19.0
Spasm of limbs	7.9	8.0
Headache	30.3	39.0
Vomiting	23.6	28.0
Diarrhea	19.1	17.0

*Source: Kuratsune et al., 1969

Yoshimura (1971) compared the growth of 42 school-aged children with Yusho (23 males, 19 females) with that of 719 sex-matched classmates described as being "healthy." For the years 1967-1969, the height and weight gains of girls with Yusho were unaffected, while boys with Yusho had significant height and weight gains.

Clinical Observations. The initial Yusho symptoms, reported among 136 patients, are summarized in Table VI-8. Based on the estimated amounts of Kanechlor-contaminated rice oil consumed in Table VI-9 and the clinical severity of resulting effects in different age groups in Table VI-10, a qualitative dose-response relationship was prepared (Kuratsune et al., 1972).

The clinical abnormalities displayed by Yu-Cheng patients were decreased red blood cell counts, increased total white cell counts and decreased hemoglobin. The patients presented with swelling of the eyelids and increased discharge from the eyes, headache, nausea and numbness of the limbs (Chang et al., 1980b).

Clinical parameters evaluating liver function were suggestive of hepatic dysfunction in both the Yusho and Yu-Cheng patients. Inverse correlation between serum bilirubin concentration in Yusho patients and blood PCB levels, with mean serum bilirubin concentrations of 0.48 ± 0.26 mg/100 mℓ in 121 Yusho patients and 0.87 ± 0.33 mg/100 mℓ in 257 healthy adult controls have been noted. Increased serum triglyceride concentration was observed in Yusho patients. Similarly, increased triglycerides and elevated activities of serum transaminases and alkaline phosphatase were recorded in the Yu-Cheng patients (Chang et al., 1980a).

TABLE VI-9

Relationship Between the Amount of Kanechlor-Contaminated Rice Oil Consumed and Clinical Severity of Yusho*

Estimated Amount of Oil Consumed	Nonaffected		Light Cases		Severe Cases		Total	
	No.	%	No.	%	No.	%	No.	%
<720 mℓ	10	12	39	49	31	39	80	100
720-1440 mℓ	0	0	14	31	31	69	45	100
>1440 mℓ	0	0	3	14	18	86	21	100

*Source: Kuratsune et al., 1972

PCB exposure in experimental animals is known to cause abnormal urinary excretion of heme precursors, thus the urinary excretion of these precursors were examined in both the Yusho and Yu-Cheng patients. PCB poisoning caused an increased excretion of delta-aminolevulinic acid (0.72-1.00 mg/24 hours) and uroporphyrin (13.6-41.2 μg/24 hours), but not in the excretion of porphobilinogen or coproporphyrin (Chang et al., 1980b). Similar studies on Yusho patients failed to reveal any differences in porphyrin metabolism; however, the studies were conducted long time after the incident (Strik et al., 1979; Nonaka et al., 1979).

Human Cancer Studies (Inhalation and Dermal Contact)

Two brief reports in the literature have noted an increased incidence of malignant melanomas in workers heavily exposed to PCBs. Bahn et al. (1976, 1977) reported two malignant melanomas in 31 research and development employees (6.5%) of a New Jersey U.S. petrochemical plant that had used Aroclor 1254 for 9 years (ending in the late 1950s). Quantified exposure levels or concentrations are not given. This incidence was significantly greater than expected ($p<0.001$), based on a person-year analysis and comparison with the Third National Cancer Survey incidence rates (NCI, 1975). Only 0.04 malignant melanomas would be expected among 31 persons for a rate of 0.13%. In a second group of 41 refinery workers exposed to "low" levels of Aroclor (quantified exposure levels not reported), one had a malignant melanoma. Exposure to other potential and known carcinogenic substances was not evaluated although they were believed to be present (Lawrence, 1977).

NIOSH (1977) expanded upon the report on New Jersey petrochemical workers by noting that eight cancers were observed in the study population of 51 research and development employees and 41 refinery plant employees reported an incidence of 0.6 cases/100,000/year (Scotto et al., 1976). The authors attribute the difference to the use of medical records at hospitals and not just tumor registry data. The county incidences over the 11-year period also did not reveal any pattern of distribution that was correlated with areas of high PCB occurrence. The authors suggest this may in part be due to small population sizes in certain areas they thought were clinically over-represented. This was compounded by the fact that fewer persons in poorer rural areas tend to seek early medical care.

Brown and Jones (1981) conducted a retrospective cohort mortality study on 2567 workers who had completed at least 3 months of employment at any time in any area of two capacitor manufacturing plants where potential for exposure to PCBs existed. PCBs had been used at the facilities for >30 years before the cut-off date of the study on January 1, 1976. Aroclor 1254 was used first but changed over the years to Aroclor 1242 and finally to Aroclor 1016. Workers exposed to trichloroethylene (TCE) were excluded from the cohort. Time-weighted average (TWA) personal air samples in the two plants ranged from 24-1260 μg PCB/m^3. Vital status ascertainment was 98% complete. Observed deaths were contrasted with expected deaths based upon U.S. white male and female deaths. All cause mortality was lower than expected in plant 1 (73 observed deaths vs. 76.7 expected) as well as in plant 2 (90 observed vs. 105.6 expected). Combining two cohorts produced a nonsignificant excess risk of liver cancer (3 observed deaths vs. 1.07 expected) and a nonsignificant excess risk of rectal cancer (4 observed deaths vs. 1.19 expected). This excess risk of rectal cancer was limited to females of plant 2 (3 observed vs. 0.5 expected).

But Brown (1986) did offer some evidence to support a causal relationship. In an environmental survey conducted in 1977 by NIOSH, and reported on in the earlier paper by Brown and Jones (1981), personal TWA exposures to PCBs (Aroclor 1016) ranged from 24 mg/m^3-393 mg/m^3 at plant 1 while at plant 2 they were higher at 381 mg/m^3-1260 mg/m^3. Four of the five liver cancers occurred in female employees at plants 2. All occurred after the 15th year of follow-up from beginning date of employment. All began working at a time when levels of exposure were likely to be highest. Furthermore, this group (Female employees at plant 2) contributed 41% of the total person-years to the analysis, the largest contribution. However, since the two plants may differ in alcohol consumption, dietary habits and ethnic composition as was pointed out by the author, it would be prudent to continue following this cohort in order to confirm that the excess risk of liver and biliary passageway cancer is real. Further analytical work on this cohort is continuing. It would be prudent to regard these findings cautiously suggestive.

Bertazzi et al. (1987) completed a retrospective prospective mortality study of 544 male and 1556 female employees of a capacitor-making facility in a small industrial town of Northern Italy. Small capacitors were made for electrical and electronic use while large capacitors were impregnated with PCBs since 1946. Aroclor 1254 and Pyralene 1476 were used until 1964. After 1964, they were progressively replaced by Pyralene 3010 and 3011 until 1970 when the lower chlorinated Pyralenes were excusively used. In 1980, the use of PCBs was completely abandoned. Maximum consumption of PCBs occurred in 1967-1968. Trichloroethylene was used in the final step of manufacturing. The workers employed in this last step are described by the

TABLE IV-11

Minimum and Maximum Values of PCBs Recovered from Workplace Surfaces and Workers Hands Before and After PCBs Banning (1980) and Cleaning Operations*

	Year	No. of Samples	Values (ug/cm^2) Min.	Max.
Workplace Surfaces	1977	18	0.2	159.0
	1982	14	0.003	6.3
Workers Hands	1977	9	0.3	9.2
	1982	12	0.09	1.5

*Source: Adopted from Bertazzi et al. (1987)

females workers were also elevated by comparison with local rates (5.3 expected, $p<0.05$). However, this excess risk did not translate into an increased significant risk of cause specific cancer. No liver or biliary cancer deaths were noted in females. Both males and females did experience an increased nonsignificant risk of hematologic neoplasms (see Table IV-12) which remains unexplained at this time.

There are several problems with this study that precludes its use at this time in upgrading the classification of the weight-of-evidence of carcinogenicity. There is an absence of significant site-specific cancer in both males and females. However, this is due to the inadequate power of the study to detect as significant an elevated risk of site-specific cancer. In actuality, this cohort needs further follow-up to determine if any trends are apparent since so few deaths have occurred by the cut-off period in this study. Latent factors were not examined probably because of the small number of deaths observed during the follow-up period. Additionally, other possible confounders may be present. Possibly trace amounts of dibenzofurans (PCDFs) may be found in the PCBs. Other substances such as trichloroethylene, alkylbenzene and epoxy resins have also been reported in the plant by the authors. Furthermore, the study does not consider the healthy worker effect in its comparison with national and local death rates nor does it analyse latent effects except on an individual case by case basis.

Human Cancer Studies (PCBs Poisoning Episodes - Ingestion Only)

Amano et al. (1984) recently completed a 16-year cohort mortality study of 1086 victims of the Yusho incident in Japan. The 581 males and 505 females sustained a total of 70 deaths (42 males vs. 45.81 expected and 28

TABLE VI-13

Risk of Death From Cancer of the Liver in Oil Poisoned Patients by Sex and Period of Observation, Japan and in Fukuoka Prefecture*

Region	Sex and Period of Observation	Observed	Expected
Japan	Males	6	1.22 (p< .01)
	1969-1976	1	0.44
	1977-1983	5	0.75 (p<0.01)
	Females	2	0.54
	1969-1976	1	0.19
	1977-1983	1	0.24
Fukuoka Prefecture	Males		
	1977-1983	3	0.66 (p<0.05)
	Females		
	1977-1983	1	0.17

*Source: Amano et al., 1984

National Japanese death rates, age-, sex- and calendar time-specific. Male expected deaths equaled 66.13, while female expected deaths equaled 48.9. Malignant neoplasms in males totaled 34 as compared with 15.51 expected ($p<0.01$). This significantly increased risk was entirely due to a significant excess risk of liver cancer (9 observed vs. 1.61 expected., $p<0.01$) and a statistically significant excess risk of cancer of the lung trachea and bronchus (8 observed vs. 2.45 expected., $p<0.01$). In females, only liver cancer appeared excessive albeit nonsignificant (2 observed vs. 0.66 expected). Even if death rates of Fukuoka and Nagasaki prefectures were used as the comparison population, the locale where the rice oil poisoning took place, the risk of liver cancer remained statistically significant.

Although the elevated risk of liver cancer is real, the authors are reluctant to attribute it to the poisoning because of the unusual distribution of deaths. In Nagasaki prefecture where some 550 patients live, only one male liver cancer patient was seen, but in Fukuoka prefecture eight liver cancers were identified out of >700 patients residing there. Deaths from liver cancer are not different from expected in Nagasaki prefecture. The authors reported that they were examining the medical records of the decedents to confirm the diagnosis of liver cancer.

Unfortunately, mortality for each prefecture is not separated; hence, it is difficult to determine if age, sex or socio-economic factors or lack of access to medical care facilities or other factors could be the reason for the differential liver cancer mortality in patients of these two prefectures. Latency was also not examined. However, the incident occurred in 1968 and affected a large number of persons with certifiable disease; hence, all live patients had to have been observed at least a minimum of 15 years.

The most important observation about this study is that another mass poisoning episode took place similar to that of the Yusho incident but it was more recent and the 2000 or so victims must be monitored and followed to determine if an excess risk of liver cancer asserts itself after a suitable latent period has lapsed. No data on cancer morbidity and mortality has been reported yet. As of this writing, 6 years is not an ample time period in which an excessive risk of liver cancer would assert itself in this cohort. In a later report Chen et al. (1981) noted as well the presence of polychlorinated dibenzofurans in samples of the toxic rice-bran oils analysed. The ratios of PCB to that of PCDF ranged from 219 to 368 to 1 in six samples.

Human Cancer Studies - Summary

Two brief reports of one study of melanoma in workers exposed to PCBs and an update of the same study by NIOSH reported a statistically significant elevated risk of melanoma based on three cases. However, it was reported that exposure to PCB could not be evaluated and that these same workers were subject to other potential carcinogens in their work.

An ecological study of incidence rates of ocular melanoma in Ohio counties revealed no pattern of association with geographic distribution of areas of high PCB concentrations. However, the measurement of exposure involved estimating the levels of PCBs in fish and the location of PCB production sites. It is highly unlikely that any positive correlation of one with the other could be determined given the methodological limitations of the design.

Amano et al. (1984) and Kuratsune (1986) reported a statistically significant excess risk of liver cancer in Yusho patients followed over 16 years in both male and female victims. The authors regard these findings as only tentative because the excess was found only in one prefecture and not the other. Furthermore, the victims consumed polychlorinated dibenzofurans and polychlorinated quinones in much smaller quantities at the same time as the PCBs. Hence exposure to these other chemicals cannot be ruled out as possible contributors to the excess risk of liver cancer in Yusho patient. These authors are refining their data at this time and reexamining their results.

Although these data seem to suggest a possible carcinogenic effect through the ingestion route and possibly inhalation route in humans, because of the tentative nature of the findings, and the fact that refinement and reevaluation of the results are underway as well as possible concurrent exposure to other potential carcinogens, CAG regards the human data at this time as inadequate but suggestive.

However, it has recently been learned (Moolenaar, 1987) that the International Agency for Research on Cancer (IARC) has classified the human health data as "limited" (2A) based upon the findings of the Bertazzi et al. (1987) and Brown (1986) studies. However, lack of site concordance and small power in these studies precludes EPA from classifying the weight of evidence higher than inadequate at this time.

High PCB serum levels were found in some women who had recent or former missed abortions with mean PCB serum levels of 103.04, 82.00 and 20.69 ppb for recent missed abortions, former missed abortions and control groups, respectively (Bercovici et al., 1983). Some women with premature delivery had mean PCB serum levels of 128 ppb in the premature delivery group vs. 26.5 ppb in the control group (Wasserman et al., 1982). The higher PCB serum levels were associated with increased incomplete abortions (Bercovici et al., 1983) and premature deliveries (Wassermann et al., 1982), but a definitive causal relationship cannot be established, as only small numbers of women were examined (up to 17 symptomatic; up to 10 asymptomatic), and some of these women had high serum levels of some organochlorine insecticides (DDT isomers and their metabolites, lindane, dieldrin, heptachlor epoxide).

Clinical Observations. PCBs were discovered in sewage sludge used for fertilizer in Bloomington, Indiana. The metabolic consequences of PCB exposure were studied (Baker et al., 1980). Serum PCB levels in sludge users were not different from those of other members of the community not using the sludge. In sludge users PCB levels were associated positively with degree of garden care and negatively with wearing gloves but not correlated with amount of sludge used or duration of exposure. Plasma triglyceride levels increased significantly with PCB concentrations.

Kreiss et al. (1981) examined 458 volunteers from Triana, Alabama, $\geq$12 years of age, and correlated serum PCB levels (Aroclor 1260) with elevated blood pressure. The mean serum PCB level among this group was 17.2 ppb.

VII. MECHANISMS OF TOXICITY

Introduction

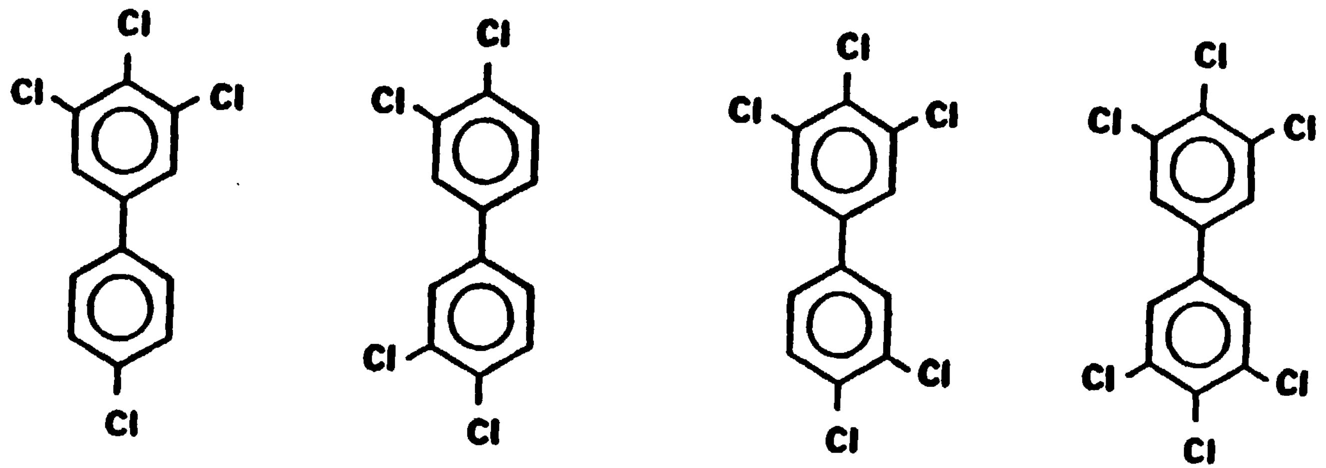
Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and naphthalenes (PCNs) are a class of structurally-related chlorinated aromatics that are industrial products or by-products and are formed during the combustion of industrial and municipal waste. The toxic and biologic effects of commercial PCB mixtures and individual isomers and congeners are dependent on a number of factors including the dose of the toxin and the sex, age, species and strain of animal used. The toxic responses observed in several animal species include a wasting syndrome, thymic atrophy and immunotoxicity, reproductive toxicity, endocrine effects, hepatotoxicity and porphyria, chloracne and related dermal lesions, carcinogenicity and the induction of diverse enzymes including several hepatic drug-metabolizing enzymes (Safe, 1984; Safe et al., 1982, 1985b; McConnell, 1980b; Kimbrough et al., 1978; Matthews et al., 1978; Poland and Knutson, 1982; Parkinson and Safe, 1981). Moreover, it has also been noted that PCBs, PCDFs, PCDDs and PCNs elicit many similar biologic and toxic responses in laboratory animals and humans, and the major differences within this class of chemical pollutants are quantitative in nature.

The proposed mechanism of action of the toxic halogenated aromatics has initially been derived from studies using the most toxic member of this class of chemicals, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The synthesis of radiolabeled [^{3}H]-2,3,7,8-TCDD with high specific activity (52.5 Ci/mmol) resulted in the identification of a specific binding protein in hepatic cytosol of "responsive" C57Bl/6J mice; in contrast minimal binding activity was observed in "non-responsive" DBA/2J hepatic cytosol (Poland

P-450d and P-450e. Phenobarbital preferentially induces cytochromes P-450b+e, 3-MC preferentially induces cytochromes P-450c and d and both compounds induce cytochrome P-450a to P-450e (Ryan et al., 1977, 1979; Botelho et al., 1979; Thomas et al., 1983).

Several studies with selected PCDD, PCDF and PCB congeners have shown that there was a rank order correlation between the toxicity of a compound and its activity as an inducer of AHH (Poland et al., 1979). Thus, induction of this enzyme activity (which is associated with cytochrome P-450c) has served as a bioassay for identifying the most toxic PCB isomers and congeners.

In vitro and *in vivo* structure-activity relationships for PCBs as inducers of AHH and cytochrome P-450c showed that the most active compounds, 3,4,4',5-tetra-CB, 3,3',4,4'-tetra-CB, 3,3',4,4',5-penta-CB and 3,3',4,4',5,5'-hexa-CB, required chlorine substitution at both para and at least two or more meta positions (Poland and Glover, 1977; Parkinson et al., 1981a). These four PCB congeners contain no ortho substituents and are all approximate isostereomers of 2,3,7,8-TCDD. Not surprisingly these compounds all bind with relatively high affinity to the cytosolic receptor protein and are also acutely toxic (Bandiera et al., 1982; Leece et al., 1985). However, analytical studies indicate that the four coplanar PCBs are minor constituents of the more active commercial PCBs, Aroclor 1254 and Aroclor 1260 (Sissons and Welti, 1971; Ballschmiter and Zell, 1980; Safe et al., 1985a; Albro et al., 1981; Mullin et al., 1981) and this fact prompted others (Safe, 1984; Sawyer and Safe, 1982; Parkinson et al., 1980a,b, 1981a,b, 1982, 1983b; Greenlee and Irons, 1981; Robertson et al., 1984) to identify the active compounds present in these mixtures.



2',3,4,4',5	2,3,3',4,4'	2,3,3',4,4',5	2,3,3',4,4',5,5'
2,3,4,4',5	2,3',4,4',5	2,3',4,4',5,5'	
		2,3,3',4,4',5'	

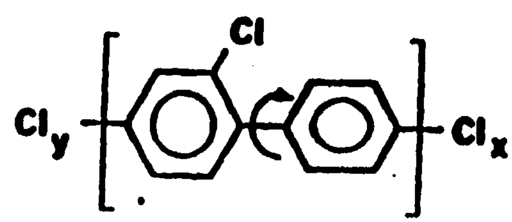


FIGURE VII-1

Coplanar and Mono-ortho Coplanar PCB Analogs

AHH or cytochrome P-450c exhibit low affinity for the receptor (EC_{50} $>10^{-5}$ M) and these values were considered nonspecific lipophilic interactions between the ligands and the hydrophobic protein binding site (Table VII-I).

PCB Toxicity -- Several studies report the toxicities of diverse PCB isomers and congeners and the results clearly demonstrate that the coplanar congeners are the most toxic group of PCB compounds. Pretreatment of rodents with the 3,3',4,4'-tetra-CB, 3,3',4,4',5-penta-CB and 3,3',4,4',5,5'-hexa-CB results in hepatic damage, porphyria, reproductive toxicity, thymic atrophy, marked increases in liver lipids, edema (in mice and chicks) and hepatomegaly (Parkinson et al., 1983b; Leece et al., 1985; Goldstein et al., 1976; Kohli et al., 1979; Biocca et al., 1981; McKinney et al., 1976; Yoshihara et al., 1979; Puhvel et al., 1982; Kawanishi et al., 1978; Swain et al., 1983; Silkworth and Grabstein, 1982; Silkworth et al., 1984). In the rhesus macaques (*Macaca mulatta*), 3,3',4,4',5,5'-hexa-CB was toxic at dietary dose levels <1 ppm whereas the 2,2',4,4',5,5'-, 2,2',4,4',6,6'- and 2,2',3,3',6,6'-hexa-CBs caused no discernible adverse effects at dose levels up to 65 ppm (McNulty, 1985); comparable structure-activity relationships were also noted in mink (Auerlich et al., 1985).

Several studies report that many of the mono-ortho coplanar PCB analogs are also toxic (Safe, 1984; Parkinson et al., 1980a,b, 1981a,b, 1982, 1983b; Bandiera et al., 1982; Leece et al., 1985; Sissons and Welti, 1971; Ballschmiter and Zell, 1980; Safe et al., 1985b; Albro et al., 1981; Mullin et al., 1981; Greenlee and Irons, 1981; Robertson et al., 1984; Goldstein et al., 1976; Kohli et al., 1979; Biocca et al., 1981; McKinney et al., 1976;

Yoshihara et al., 1979; Yamamoto et al., 1976; Ax and Hansen, 1975). For example, 2,3,3',4,4'-penta-CB administered to mice results in a wasting syndrome (weight loss), edema, liver lipid accumulation, extensive hepatic damage, and splenic atrophy, 2,3',4,4',5-penta-CB causes 100% embryo mortality in eggs from pullets receiving the PCB in their diet at a level of 20 ppm (Ax and Hansen, 1975); administration of 2,3',4,4',5-penta-CB and 2,3,3',4,4',5-hexa-CB to rats causes increased liver weights, increased liver lipids and thymic atrophy; 2,3,3',4,4',5-hexa-CB, 2,3,4,4',5-penta-CB, 2,3,3',4,4',5'-hexa-CB, 2,3,3',4,4',5'-hexa-CB and 2,3,3',4,4'-penta-CB cause thymic atrophy in male rats. Quantitative structure-activity relationships for several coplanar and mono-ortho coplanar PCBs has recently been reported (Leece et al., 1985). A comparison of the ED_{50} values for AHH/ethoxyresorufin O-deethylase (EROD) induction, body weight loss and thymic atrophy in the rat clearly demonstrates the higher toxicity of the formed group of compounds. Moreover, there was an excellent linear correlation between the in vitro AHH/EROD induction potencies of these compounds and their in vivo toxicities and AHH/EROD induction potencies.

The data indicate that the mono-ortho analogs of the coplanar PCBs elicit toxic effects that resemble (qualitatively) 2,3,7,8-TCDD; several of these compounds (2,3,3',4,4'-penta-CB, 2,3',4,4',5-penta-CB and 2,3,3',4,4',5-hexa-CB) have been identified in commercial PCBs and as residues in human tissues (Sissons and Welti, 1971; Ballschmiter and Zell, 1980; Safe et al., 1985a; Albro et al., 1981; Mullin et al., 1981).

The toxicity of the di-ortho coplanar PCBs has not been systematically investigated; however, two members of this group, 2,2',3,3',4,4'- and et al., 1983). These experiments with inbred mice also demonstrate that the presence of the receptor in the species also influences response specificity to the biologic and toxic effects of PCBs.

Summary. The genetic studies with inbred mice and the extensive structure-function relationships summarized previously support the proposed receptor-mediated mechanism of action for PCBs and related toxic halogenated aryl hydrocarbons. The precise role of the receptor ligand complex has been determined for the induction of cytochrome P-450c (Tukey et al., 1981; Israel and Whitlock, 1984; Jones et al., 1985) and involves nuclear translocation of the ligand receptor complex, interaction with nuclear binding site(s) followed by induction of the mRNA for cytochrome P-450c. Although the initial toxin-receptor interactions are probably involved in the ultimate expression of some of the toxic effects of PCBs, 2,3,7,8-TCDD and related compounds, the subsequent steps that lead to the diverse toxic responses have not been delineated.

Role of Metabolism in PCB Toxicity

Although PCBs produce a number of diverse toxic responses in a number of organs, the chemical species responsible for the toxicity are not known. It has been suggested that the parent compound, reactive intermediates formed during metabolism and metabolites of PCBs all produce toxic effects. For example, it was suggested that PCB-induced porphyria was produced by the parent compound (Strik et al., 1979). Other investigators have suggested that the cytotoxic and mutagenic effects of PCBs result from reactive arene oxides that are formed during metabolism (Allen and Norback, 1977; Wyndham et al., 1976). PCBs that contain vicinal unsubstituted carbon atoms are lipophilic metabolites formed during biotransformation of PCB by the mercapturic acid pathway. These metabolites have been found to selectively accumulate in the apical cytoplasm of nonciliated bronchiolar (Clara) cells of the rat lung (Lund et al., 1985). This selective _in vivo_ uptake appears to be due to the presence of a protein with high affinity and capacity for binding PCB methyl sulfones. This binding protein is present in Clara cells and the tracheobronchoalveolar lavage fluid from rats, mice and humans (Brandt, 1986; Lund et al., 1986a). Methylthio and methylsulfonyl PCBs have been identified in lung tissue from Yusho patients and healthy controls (Haraguchi et al., 1984, 1986). Lund et al. (1986a) proposed that the binding protein was responsible for the observed tendency of these PCB metabolites to accumulate in the lung tissue of humans. While the toxicological significance of these findings is not known, it has been suggested that these metabolites may be in part responsible for the persistent respiratory distress seen in the victims of PCB poisonings in Japan (Yusho) and the decreased lung vital capacity in workers exposed to PCBs (Shigematsu et al., 1978; Warshaw et al., 1979). In apparently the only study on the effect of PCB metabolites on lung function, Lund et al. (1986b) reported that 4-methylsulphonyl-2,2',5,5'-tetra-CB inhibited a cytochrome P-450-dependent enzyme activity in mouse lung, while inducing this activity in mouse liver. Thus, while these results suggest that PCB metabolites may mediate specific toxic responses of PCBs, further studies are needed to confirm the role of metabolism in the expression of toxicity.

Other Mechanisms

It is apparent that many PCB isomers and congeners that do not bind to the 2,3,7,8-TCDD receptor protein elicit a broad spectrum of biologic and

Summary

Data on purified PCB isomers have established that the toxic, metabolic and toxicokinetic behavior of the different component molecules varies not only with the degree of chlorination (greater toxic potency with greater degree of chlorination) but also with the position of the chlorine atoms. The relative toxicity and persistence of four pure hexa-CB isomers was examined in mice; 3,4,5-sym-hexa-CB was found to be the most toxic (LD_{50} = 19 mg/kg bw/day) and persistent (levels in liver and adipose tissue) isomer, followed by 2,4,6-sym-hexa-CB > 2,4,5-sym-hexa-CB, > 2,3,6-sym-hexa-CB. Although structure-activity relationships are most interesting for this class of compounds, it is also important to note that highly toxic, coplanar PCB isomers, such as 3,4,5-sym-hexa-CB, have only been detected as very minor constituents of commercial PCB formulations.

the U.S. EPA (1986a) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

Group A: <u>Human Carcinogen</u>. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.

Group B: <u>Probable Human Carcinogen</u>. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.

Group C: <u>Possible Human Carcinogen</u>. Limited evidence of carcinogenicity in animals in the absence of human data.

Group D: <u>Not Classified as to Human Carcinogenicity</u>. Inadequate human and animal evidence of carcinogenicity or for which no data are available.

Group E: <u>Evidence of Noncarcinogenicity for Humans</u>. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

The evidence of human exposure to PCBs from finished drinking water is limited. A single finished groundwater sample in each of the National Organic Monitoring Survey (NOMS) II and III contained PCBs in minimum quantifiable detectable limits that ranged from 0.1-0.2 μg/ℓ, respectively. PCBs were detected in all three phases of the NOMS of finished surface water. In this survey of finished surface drinking water, PCBs were detected in two samples of NOMS I at levels of 0.13 and 1.4 μg/ℓ; in NOMS II, two samples contained 0.1 μg/ℓ and one sample had 0.2 μg/ℓ of PCBs; and only one sample of NOMS III contained PCBs at a concentration of 0.2 μg/ℓ. Schroeder and Barnes (1983) showed that PCB removal from Hudson River water ranged between 80 and 90% with levels in finished drinking water seldom exceeding 100 ng/ℓ. Congeners of Aroclor 1016 were also detected in finished drinking water with the Hudson River as its source at a median concentration of 85 ng/ℓ (Brinkman et al., 1981).

1254). Thus, 10 of the 19 congeners selected were unambiguously from Aroclor 1016, with 6 being resolved specific congeners. In this study, 60 congeners were utilized to identify the possible presence of Aroclors 1221, 1016, 1254 and 1260. Each peak chosen provided an independent estimate of the quantity of the Aroclor using the appropriate response factor for each congener. The concentration of the Aroclor was calculated as the average of the concentrations by each of the five chosen peaks. Representative samples were confirmed by GC/MS. The detection limit was 50 pg, equivalent to a 12 ng/ℓ (12 ppt) concentration in 2 ℓ of water subjected to the analysis technique.

It is clear the least chlorinated congeners are the PCBs that might be expected to occur in drinking waters produced from nonchlorinated processes. Chlorination may lead to the presence of higher chlorinated PCBs for Aroclor 1221 and below but not for Aroclor 1242 and above (Aly and Badawy, 1986). Most of the residues in human tissues are highly chlorinated (Holt et al., 1986; Ansari et al., 1986; Safe, 1984; Bush et al., 1985b). This is characteristic of exposure through food sources such as fish, birds or human milk. The less chlorinated congeners dominate in inhalation and drinking water exposures.

PCBs in the Hudson River (from Aroclors 1221, 1242, 1248, 1254 and 1260) are still at levels causing concern (Brown et al., 1985; Bush et al., 1985a). The more soluble less chlorinated congeners dominated in waters without sediments, and the highly chlorinated congeners were associated with particulate matter (Bush et al., 1985a; Brown et al., 1985; Baker et al., 1985). This also applied to wet deposition (Mazurek and Simoneit, 1985).

Ringer, 1977). Route of administration also had little effect (<1 order of magnitude) on lethality with the lethal dose for dermal administration in rabbits ranging from 0.8-3.2 g/kg bw (Nelson et al., 1972); while the lethal dose in mice administered PCBs by i.p. injection, ranged from 0.9-1.2 g/kg bw (Lewin et al., 1972). The role of the toxic PCDF impurities in these effects is unknown.

There are two indications of major differences in the acute toxicity of PCBs. First, there is limited evidence that the guinea pig may be more sensitive to the lethality of PCBs than other species. This species is also more sensitive to toxic PCDFs. Miller (1944) observed 100% mortality in a small group of guinea pigs receiving two oral doses of PCB (43% chlorine) at levels of 67 mg/animal at 7-day intervals. In a study with perhaps the most potent PCB isomer, McConnell and McKinney (1978) reported a LD_{50-30} of 0.5 mg/kg bw for 3,4,5-sym-hexa-CB in guinea pigs. This indication of possible large interspecies differences in sensitivity is of concern in species-to-species extrapolation when there is insufficient data to indicate which experimental animal most accurately reflects the sensitivity of humans. The second problem concerns the possible large difference in toxicity of specific congeners and isomers of PCBs. Limited mortality data were available from a study by Biocca et al. (1981), in which four different hexa-CBs were administered in the diet to mice for 28 days. They reported LD_{50-28} values ranging from 86.8 ppm (19 mg/kg bw/day) to >300 ppm (>64 mg/kg bw/day), with 3,3',4,4',5,5'-hexa-CB being the most potent and persistent isomer investigated. Probably even larger differences will be encountered as more congeners and isomers are tested. It is expected that the lower chlorinated congeners will be eliminated more quickly in humans than the highly chlorinated ones.

Besides changes in the liver, other effects reported for exposure to low levels of PCBs were increased thyroid activity in Sherman rats maintained on diets containing 250 ppm of Aroclor 1254 (12.5 mg/kg bw) for 14 days. Administration of Aroclor 1254 by gavage for 21 days at a dose of 0.05 g/kg bw/day resulted in weight loss and decreased body temperature in Sprague-Dawley rats (Komives, 1979; Komives and Alayoku, 1980). Ultrastructural evidence suggesting increased thyroid gland activity has also been found in Osborne-Mendel rats maintained on diets containing 5 ppm of Aroclor 1254 (0.25 mg/kg bw/day) for 4 weeks (Collins and Capen, 1980b). This exposure level also resulted in increased liver enzymes in Holtzman rats (Garthoff et al., 1977).

The toxicity resulting from PCB exposures of between 30 and 90 days has been more extensively studied. Alterations in liver ultrastructure occurred at doses of Aroclor 1254 as low as 5 ppm diet for 5 weeks in Holtzman rats (Kasza et al., 1978b). In the mouse (MNRI) a dose of Clophen A-60 as low as 0.025 mg/mouse (0.8 mg/kg bw/day, assuming a mouse weight 0.03 kg) for 62 days increased the estrous cycle, probably as a result of PCB-induced changes in liver steroid metabolism (Orberg and Kihlstrom, 1973). At higher dietary concentrations of 167 ppm (22 mg/kg bw) for 6 weeks, Aroclor 1016 and 1242 decreased the immunologic capability of BALB/CJ mice (Loose et al., 1978a).

Although other species have been tested to a lesser extent for this duration, the LOEL in these species were similar to those described for rats and mice. Rabbits exposed to diets containing 3.7 ppm of Aroclor 1254 (0.18 mg/kg bw/day, assuming a rabbit consumes 4.9% of its body weight/day) for 8 weeks developed no significant hepatomegaly, although atrophy of the

In mice dietary exposure levels to Kanechlor-300, -400, or -500 or Aroclor 1254 of between 100 and 500 ppm (13-65 mg/kg bw/day) for periods from 23 weeks to 11 months produced hepatomegaly (Ito et al., 1973; Bell, 1983; Kimbrough and Linder, 1974). The only study that defined a NOAEL in mice was the study by Koller (1977). Groups of BALB/CJ mice were maintained for 9 months on diets containing 0, 3.75, 37.5 or 375 ppm of the Aroclors 1221, 1242 or 1254 (0.45, 4.57 or 45.7 mg/kg bw/day). Aroclor 1221, with the lowest chlorine content (21%), produced no liver lesions, while exposure to Aroclor 1242 (42% chlorine) resulted in increased liver weight in the high-dose group. In mice exposed to Aroclor 1254, increased mortality was observed in the high-dose group with mild hepatopathology being observed in the median-dose group, and no liver lesions detected in the low-dose group. The NOEL observed in this study in mice of 0.45 mg/kg bw/day is nearly identical to the LOELs of 0.5 mg/kg bw/day associated with porphyria in rats (Zink, 1977), or 0.25 mg/kg bw/day associated with ultrastructural evidence suggesting increased thyroid gland activity (Collins and Capen, 1980b).

The only other species tested in chronic bioassays was the monkey and it proved to be highly sensitive to the toxic effects of PCBs. The most common observation in monkeys exposed to Aroclor 1248 in the diet for a period of from 8-39 months was skin lesions, edema and erythema (Barsotti and Allen, 1975; Allen and Barsotti, 1976; Allen et al., 1980; Becker et al., 1979). These effects were observed at the lowest doses tested [2.5-3 ppm in the diet (0.095-0.126 mg/kg bw/day)]. In addition, Becker et al. (1979) reported that monkeys fed diets containing 3 ppm of PCBs had gastric lesions, body weight loss and reduced hemoglobin and leukocytes.

water (Baker et al.. 1977). Males regained normal fertility after removal from treatment for 2 weeks. When Aroclor 1254 was administered to lactating Holtzman rats at 32 mg/kg bw/day on days 3, 5 and 7 of lactation, the future mating behavior of nursing male pups was adversely affected (Sager, 1983). A lower dose of 8 mg/kg bw/day was a NOEL.

The mink and the monkey are the most sensitive species tested to the reproductive toxicity of the PCBs. Bleavins et al. (1980) maintained mink on diets containing 5 ppm Aroclor 1242 or 20 ppm Aroclor 1016 (doses of 0.75 and 3 mg/kg bw/day, assuming a mink consumes 15% of its body weight per day) for 8 months and observed complete reproductive failure in the Aroclor 1242 group and 25% mortality and infertility in the Aroclor 1016 group. In a limited study (8 animals/group), Barsotti et al. (1976) maintained rhesus monkeys on diets containing 2.5 or 5 ppm (0.1 or 0.2 mg/kg bw/day) of Aroclor 1248 for 18 months. In the low-dose group, all eight females conceived, but only five delivered viable infants. In the high-dose group, the mothers showed overt signs of toxicity. In the 5.0 ppm group, 6 of 8 females conceived, but only one live birth occurred. After removal from exposure for 1 year, reproductive capabilities appeared to return to normal; however, an increase in abortion rate and infant mortality was observed for both PCB treatment groups (Allen et al., 1980). It is apparent that frank effects in reproduction were observed in monkeys at lower doses than the NOEL in rats, rabbits and guinea pigs following repeated exposure to PCBs. Little data are available for the toxicity of specific congeners. Dietary exposure to as little as 1 ppm of pure 3,4,5,3',4',5'-hexa-CB for 28 days caused liver microabscesses and an increased liver weight in 18-20 g 5-week-old C57Bl/6J mice (Biocca et al., 1981). In this study, dietary exposure at

Utilizing a dose of 1 mg/kg bw as a no-adverse-effect dose, a 10-day exposure level to PCB-contaminated soil may be calculated as follows (U.S. EPA, 1986b):

$$\text{10-day exposure level} = \frac{1\ \text{mg/kg/day} \times 10\ \text{kg}}{100} = 0.1\ \text{mg/day}$$

where:

10 kg = assumed body weight of a child

100 = uncertainty (safety) factors; this uncertainty factor was chosen in the accordance with the National Academy of Sciences guidelines in which a NOAEL from an animal study is employed.

This 10-day exposure level of 0.1 mg/day may be applied for a 10-day HA for drinking water if it is assumed that Aroclor 1254 mixtures are soluble and detected in drinking water. This assumption is probably not correct since the less chlorinated congeners are much more soluble than the highly chlori- nated ones and Aroclor 1254 has not yet been detected in finished drinking water.

The finished water from the Dority Reservoir treatment and distribution system was reported to contain Aroclor 1016 congeners at a level of 86 ng/ℓ (Brinkman et al., 1981). The public water supply system of the village of Fort Edward, located near the township of Moreau of Saratoga County in upstate New York, is obtained from the Dority Reservoir treatment and distribution system. The level of Aroclor 1016 in this finished water corresponded well to the median level of 99 ng/ℓ in the Dority River water. The Brinkman et al. (1981) study was discussed earlier in Chapter IV.

In another study, Aulerich and Ringer (1977) exposed female minks through diet containing 2 ppm Aroclor 1016 for 10 months (0.3 mg/kg bw/day, assuming a mink consumes 15% of its body weight per day). This level of exposure produced no effect on reproductive parameters, kit growth, and adult and kit mortality. Thus, chronic exposure to 2 ppm Aroclor 1016 in the diet (0.3 mg/kg bw/day) appears to be a NOAEL in the mink. Barsotti and Van Miller (1984) exposed 24 adult rhesus monkeys to diets containing Aroclor 1016 at levels of 0.025, 0.25 and 1.0 ppm. No abnormalities were noted in clinical, growth and reproductive parameters of the adult monkeys. The infants born to the 1.0 ppm Aroclor 1016 group (0.042 mg/kg bw/day, assuming a monkey consumes 4.2% of its body weight per day) were significantly smaller than the control at a confidence level of 99%. Thus, 0.25 ppm (0.0105 mg/kg bw/day) appears to be a NOAEL for chronic oral exposure to Aroclor 1016 in rhesus monkeys.

Utilizing a dose of 0.01 mg/kg bw/day (0.25 ppm) as the NOAEL, the longer-term HA for Aroclor 1016 may be calculated as follows:

$$\text{RfD} = \frac{0.01 \text{ mg/kg/day}}{100} = 0.0001 \text{ mg/kg/day}$$

where 100 = uncertainty (safety) factor. This uncertainty factor was chosen in accordance with the National Academy of Sciences guidelines in which a NOAEL from an animal study is employed.

Longer-term HA for a 10 kg child:

$$= \frac{0.0001 \text{ mg/kg/day} \times 10 \text{ kg}}{1 \text{ ℓ/day}}$$

$$= 0.001 \text{ mg/ℓ}$$

3) postnatal deficiencies could possibly occur at levels of exposure lower than those required for effects on structural development or viability. These and other similar studies will be reviewed for their impact on the assessment of developmental and reproductive effects and will be added to the document where appropriate.

Carcinogenic Effects

There are several studies demonstrating that PCBs cause cancer in laboratory animals. Male dd mice fed Kanechlor 500 developed hepatocellular carcinomas and liver nodules (Ito et al., 1973). Male BALB/CJ mice fed Arochlor 1254 developed hepatomas or liver adenofibrosis (Kimbrough and Linder, 1974). Female Sherman rats fed Arochlor 1260 developed hepatocellular carcinomas and neoplastic nodules (Kimbrough et al., 1975). Male and female Fischer 344 rats fed Arochlor 1254 developed hepatocellular carcinomas (NCI, 1978). Although NCI's results are not statistically significant, they are considered supportive because the small sample sizes limit the study's power to show a significant response and because there is a dose-response trend. Male Wistar rats fed Clophen A60 developed hepatocellular carcinomas (Schaeffer et al., 1984). Male and female Sprague-Dawley rats fed Arochlor 1260 developed hepatocellular carcinomas (Norback and Weltman, 1985).

These studies provide sufficient evidence regarding the carcinogenicity of PCBs. Liver cancer has been induced in several studies in different animal strains fed several commercial PCB products. The contention that these results are due to the PCDF contamination of PCBs is refuted by the

Data Selection. Human studies, although suggestive of a link between PCBs and certain types of cancer, are not yet suitable for quantitative cancer risk estimation. Consequently, risk estimates must at this time be based on animal studies. The most sensitive animal species tested appears to be the rat. In the past the U.S. EPA has based its risk estimates on a study by Kimbrough et al. (1975) in which chronic dietary administration of Aroclor 1260 was shown to cause hepatocellular carcinomas in female Sherman rats. The following analysis, however, is based on a study by Norback and Weltman (1985) in which chronic dietary administration of Aroclor 1260 was shown to cause hepatocellular carcinomas in male and female Sprague-Dawley rats. This recent study is preferred because the Sprague-Dawley rat has a low incidence of spontaneous hepatocellular neoplasms, because the Norback and Weltman (1985) study spanned the natural life of the animal, and because concurrent morphologic liver studies showed the sequential progression of liver lesions to hepatocellular carcinomas. Because neoplastic nodules have been shown to precede carcinomas, animals with neoplastic nodules were counted with those developing carcinomas. The tumor incidences for female rats, which were more sensitive than the males, are presented in Table VIII-1. The average levels (in ppm) of PCDFs in Aroclor 1260 are typically: TCDF, 0.2-0.8; PeCDF, 0.3-0.9; hexa-CDF, 0.3-0.5 (see Table II-3). The levels (in ng/g) of 2,3,7,8-substituted toxic isomers are: TCDF, 0.84; PeCDF, 2.1; hexa-CDF, 2.4 (see Table II-5). The toxic PCDFs are analogues of 2,3,7,8-TCDD, which is a known animal carcinogen. The role of the PCDFs in PCB toxicity and carcinogenesis is still unknown. The following dose-response treatment will not consider the contribution of the PCDFs.

__Dose-Response Modeling__. Current available evidence on the metabolism and kinetics of PCBs is insufficient to support the existence of nonlinear mechanisms for the development of PCB-induced cancer. In the absence of evidence to the contrary, the U.S. EPA uses the linearized multistage model to estimate increased cancer risks. The dose data are derived through the following sequence of transformations. First the nominal dose level of 100 ppm in the diet is expressed as 5 mg/kg/day, assuming that a rat consumes an amount equal to 5% of its body weight each day. Then this nominal dose is transformed into a TWA daily dose of 3.45 mg/kg/day, which reflects the dosing schedule of 5 mg/kg/day for the first 16 months, half of that for the next 8 months, and none for the last 5 months. Finally, this average daily dose is transformed into an equivalent human dose of 0.59 mg/kg/day, which reflects an equivalence between species on the basis of relative body surface areas.

The U.S. EPA sometimes uses other mathematical dose-response models to provide alternate risk estimates for comparison. This cannot be done with the preferred data set because the number of dosed groups (one) does not permit the estimation of two or more parameters as required by the other models. In particular, with only one dosed group the multi-hit model with one hit and the Weibull model with shape parameter equal to 1 are identical to the multistage model used here.

__Potency Estimation__. Using the data described above and the linearized multistage model, the human carcinogenic potency of Aroclor 1260 is estimated at 7.7 mg/kg/day. For small exposures (those for which the risk is <10%) the increased cancer risk can be estimated by multiplying the potency

TABLE VIII-2

Data Used as the Basis for an Alternate Potency Calculation for Aroclor 1260†

Sex, strain, species	Female Sprague-Dawley rat	
Exposure route, vehicle	Oral, diet	
Tumor site, type	Liver, trabecular carcinoma/adenocarcinoma	
Nominal Dose	0	100 ppm
Average daily dose	0	3.45 mg/kg/day (5% food rate assumed)
Equivalent human dose	0	0.59 mg/kg/day (surface-area corrected)
Tumor incidence	0/49	43/47
Body weight	350 g (assumed)	
Exposure duration	24 months (dose halved during months 17-24)	
Study duration	29 months	
Animal lifespan	29 months (assumed)	
Potency (q_1*)	5.7 per mg/kg/day	

†q_1* derived from Norback and Weltman (1985) study.

TABLE VIII-3

Data Used as the Basis for the Previous Potency Calculation for Aroclor 1260†

Sex, strain, species	Female Sherman rat	
Exposure route, vehicle	Oral, diet	
Tumor site, type	Liver, hepatocellular carcinoma/neoplastic nodule	
Nominal Dose	0	100 ppm
Average daily dose	0	4.57 mg/kg/day (5% food rate assumed)
Equivalent human dose	0	0.78 mg/kg/day (surface-area corrected)
Tumor incidence	1/173	170/184
Body weight	350 g (assumed)	
Exposure duration	21 months	
Study duration	23 months	
Animal lifespan	23 months (assumed)	
Potency (q_1*)	3.9 per mg/kg/day	

†q_1* derived from Kimbrough et al. (1975) study.

Cancer Potency Estimates for AroclorR 1254 and other PCB mistures

Because exposure assessments sometimes find PCB mixtures that resemble PCB products other that Aroclor● 1260, it is often asked whether separate cancer potency estimates can be made for other PCB mixtures. Although the best data base for estimating the cancer potency is on Aroclor● 1260, it is appropriate to ask whether existing data on other PCB mixtures are adequate for making separate cancer potency estimates.

A natural candidate for a separate cancer potency estimate is Aroclor● 1254. An estimate can be based on the 1978 National Cancer Institute (NCI) study of Aroclor● 1254, in which statistically significant, dose-related increases in liver nodules, benign tumors, and malignant tumors combined were seen in Fischer 344 rats fed a diet containing Aroclor● 1254. Preliminary calculations would indicate a cancer potency of 2.6 per mg/kg/day continuous lifetime exposure to Aroclor● 1254. This estimate is a plausible upper bound, meaning that the true cancer potency is not likely to exceed this estimate and may be lower. Details of the study and the potency calculation are given in Table VIII-4.

Several sources of uncertainty deserve mention:

1. NCI used only 24 rats per group (50 is considered standard today), so the potency estimate is rather imprecise.

2. The NCI study lasted 24 months. Although this is today's standard, Norback and Weltman demonstrated that PCB-fed rats (but not control rats) develop many tumors after 24 months. EPA considers the Norback and Weltman study more appropriate for estimating a lifetime cancer potency.

3. NCI's female rats developed only benign liver tumors and nodules, so some may argue that there was no cancer. Norback and Weltman, however, demonstrated that nodules progress to benign tumors, which in turn progress to malignant tumors. Under EPA's cancer guidelines it is, therefore, appropriate to consider benign tumors and nodules. Furthermore, some male rats in the NCI study did develop malignant liver tumors.

EPA's cancer potency for Aroclor● 1260, which is presumed to apply to other PCB mixtures as well, is 7.7 per mg/kg/day continuous lifetime exposure. Although it appears that the cancer potency of Aroclor● 1254 may be slightly less than that of Aroclor● 1260, this difference may not be real in light of the uncertainties cited above. Larger differences are commonly seen between different sexes and animal strains. For example, a comparison of the NCI and Norback and Weltman studies suggests that Aroclor● 1254 may be <u>more potent</u> in male Fischer 344 rats than Aroclor● 1260 is in male Sprague-Dawley rats. For these reasons, the current data are inadequate to differentiate between these PCB mixtures with any reasonable degree of confidence.

isomers (Wszolek et al., 1979; Brown et al., 1985). Food chain vectors also are important in the congeners bioaccumulated (Bush et al., 1985a). The Food and Drug Administration (FDA) has set tolerances for PCBs in food and food related products as indicated in Table VIII-5.

Occupational exposure limits have been recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 1980), and a recommended criterion set by the National Institute for Occupational Safety and Health (NIOSH, 1977) for PCBs in the workroom air. The TWA and STEL for Aroclor 1254, respectively, are 0.5 and 1.0 mg/m^3; and 1 and 2 mg/m^3 for Aroclor 1242 (ACGIH, 1980). The NIOSH (1977) recommended criterion for PCBs is 1.0 μg/m^3 for all PCBs for a 10 hours/day, 40 hours/week exposure. The OSHA permissible exposure level (PEL) and immediately dangerous to life and health level (IDLH) for Aroclor 1242 are 1 and 10 mg/m^3, respectively, and 1 and 5 mg/m^3 for Aroclor 1254 (NIOSH, 1977).

The NAS (1980) developed a 24-hour SNARL for PCBs of 350 μg/ℓ based on the induction of mixed-function oxidase enzymes in the liver of rats administered Aroclor 1254 at doses of 1-2 mg/kg. For this analysis, an uncertainty factor of 100 was used, since only enzyme induction was reported in this dose range.

<u>Summary</u>

A recommendation was not made at this time for 1-day or 10-day HAs or a DWEL because of a deficient data base on toxicity and exposure to PCBs through drinking water in the United States. A longer-term HA for Aroclor 1016 for a child has been estimated to be 0.001 mg/ℓ and for an adult

0.0035 mg/L. A cancer based criterion for Aroclor 1260 was derived and calculated for excess lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6}. The respective water concentrations are 0.5, 0.05 and 0.005 μg/L (Table VIII-6). If Aroclor 1260 is detected in the finished drinking water then the cancer based criterion may be applied. A decision to utilize the cancer potency estimate from Aroclor 1260 to characterize the upper limit risks and or calculate specific drinking water criteria for other PCB mixtures is risk assessment option (policy choice).

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